# Postgraduate Medicine

*Volume 30 · Number 2*

AUGUST · 1961

OFFICIAL JOURNAL OF THE INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION


## TABLE *of* CONTENTS


Auto-immune Disease: Some General Principles
FRANK MACFARLANE BURNET, O.M., F.R.S. . . . . 91

Early Recognition and Treatment of Hepatitis
WILLIAM D. DAVIS, JR., M.D. . . . . 96

Viral Diseases; Their Control by Immunologic Means
JONAS E. SALK, M.D. . . . . 99

A Biochemical Concept of Mental Disease
WILLIAM M. McISAAC, M.B., PH.D. . . . . 111

Office Diagnosis of Congenital Malformations of the Heart, Part 1
BENJAMIN M. GASUL, M.D., RENE A. ARCILLA, M.D. AND
MAGNUS H. AGUSTSSON, M.D. . . . . 119

Sudden Death From Coronary Disease—the Cardiac Conundrum
LESTER ADELSON, M.D. . . . . 139

**PHYSICAL MEDICINE AND REHABILITATION**

Self-help Devices: Homemaking: Dishwashing
EDWARD W. LOWMAN, M.D. AND HOWARD A. RUSK, M.D. . . . . 148

**NUTRITION**

Management of Acute Renal Failure
W. A. KREHL, M.D. . . . . 150

**SCIENTIFIC EXHIBIT**

Cancer; Prevention of Dissemination
WILLIAM J. GROVE, M.D., STUART S. ROBERTS, M.D., LEROY LONG, M.D.,
OLGA M. JONASSON, M.D. AND WARREN H. COLE, M.D. . . . . 157


*(Continued on page A-4)*


**Postgraduate Medicine** is published monthly at Minneapolis, Minn., by IPMA Publishing Co., G. Victor Lowrie, executive vice-president; William H. Hull, professional relations manager; Muriel D. Ries, circulation manager; Fred Couzens, Eastern manager, 420 Lexington Ave., New York 17, N.Y., telephone Murray Hill 4-7752; Arthur G. Sullivan, Jr., Central-West manager, 203 North Cedar Street, Horicon, Wis., telephone Hunter 5-2003. Advertising representatives: McDonald-Thompson, 1008 Western Ave., Seattle 1, Wash.; 625 Market St., San Francisco 5, Calif.; 3727 W. 6th St., Los Angeles 5, Calif.; 2727 Oak Lane Ave., Dallas 19, Tex.; 3217 Montrose Blvd., Houston 6, Tex.; 620 Sherman St., Denver 3, Colo. Publication date: 10th of the month. Subscription rate $10.00 a year in the United States and Canada; $12.00 in foreign countries. Two volumes a year. Address all editorial and business correspondence to **Postgraduate Medicine**, Essex Building, Minneapolis 3, Minn., telephone Federal 9-8836.

© 1961 by IPMA Publishing Co.
Title Reg. U. S. Pat. Off. Second-class postage paid at Minneapolis, Minnesota and at additional mailing offices. Printed in U.S.A.

**CLINICOPATHOLOGIC CONFERENCE**

Recurrent Jaundice and Coma
FROM THE VETERANS ADMINISTRATION HOSPITAL, HINES, ILLINOIS ..... 164

**DEPARTMENTS**

EDITORIALS ..... 171
*Brain Research*
*Adrenocortical Response of Bantu and Europeans to Surgical Stress*

FORTHCOMING FEATURES ..... A-9

PROBLEMS AND SOLUTIONS ..... A-12
*Phenylketonuria*
*Labor-Inducing Drugs*
*Angina*
*Breech Presentation*

LABORATORY NOTES ..... A-18
Current Status of Tests of Adrenocortical Function, Part 2
JAMES C. MELBY, M.D.

WHAT'S HAPPENING IN MEDICINE ..... Facing A-32

FORENSIC MEDICINE ..... A-42
Blunt Violence
FRANCIS J. HATCH, M.D.

MEETINGS AND POSTGRADUATE COURSES ..... A-56, 118

RADIOLOGY ..... A-59
X-ray Technic
PAUL C. HODGES, M.D.

MEDICINE FROM ABROAD ..... A-69

GREAT NAMES IN AMERICAN MEDICAL HISTORY ..... A-86
Alexander M. Tuthill, M.D., Arizona

NEW FOR YOUR ARMAMENTARIUM ..... A-94

THE MEDICAL BOOKMAN ..... A-103

THE MEDICAL MUSE. Richard Armour ..... A-106

YOUR FINANCES ..... A-115
Financial Planning for the Medical Practitioner

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY PROGRAM ..... A-132

DR. PEPYS' PAGES. Morris Fishbein, M.D. ..... A-140

INDEX TO TECHNICAL EXHIBITS ..... A-149

FORTHCOMING FEATURES

# IN Postgraduate Medicine

**Management of Severe Toxemia of Pregnancy**

MILTON L. MCCALL, M.D., University of Pittsburgh School of Medicine, Pittsburgh

**Use and Abuse of X-ray Therapy for Benign Skin Conditions; With Particular Reference to X-ray Atrophy**

DONALD M. PILLSBURY, M.D., University of Pennsylvania School of Medicine, Philadelphia

**Primaquine-Sensitive Type of Drug-Induced Hemolytic Anemia**

WILLIAM H. ZINKHAM, M.D., The Johns Hopkins Hospital, Baltimore

LABORATORY NOTES

**Pure Water**

DOUGLAS A. NELSON, M.D., University of Minnesota Medical School, Minneapolis

NUTRITION

**Obesity, Drugs and Formula Diets**

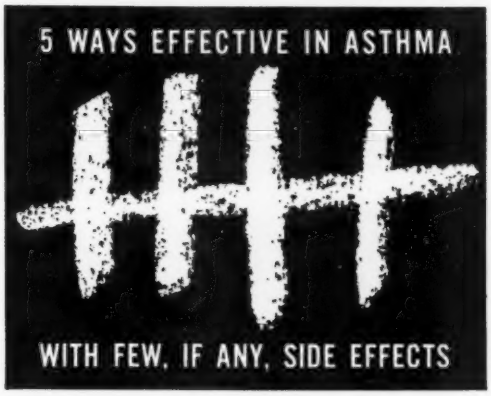
SAMI A. HASHIM, M.D., Institute of Nutrition Sciences, Columbia University, New York

RADIOLOGY

**Small Hiatus Hernia, Gastroesophageal Regurgitation and the Phrenic Ampulla**

FREDERIC E. TEMPLETON, M.D., University of Washington School of Medicine, Seattle

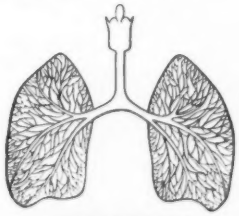

BRONKOTABS®




/ clears the bronchial tree of thick mucus
// dilates bronchioles; relieves bronchospasm
/// reduces respiratory distress
//// allays anxiety
-/// controls associated allergic symptoms

82% of patients treated with BRONKOTABS experienced relief in a new study which also reported, "The combination of drugs used (BRONKOTABS) in this study gave greater relief...than the conventionally used tablets which did not contain an antihistamine and an expectorant."(1)

In another recent study of 64 asthmatic patients 94% evidenced symptomatic relief with BRONKOTABS.(2)



BRONKOTABS
CLEARS AND DILATES
THE BRONCHIAL TREE

**Dosage:** Marked and consistent relief of symptoms is achieved with a dose of one tablet every three or four hours, not to exceed five times a day. Children over six, one-half the adult dose. Children under six: BRONKOTAB ELIXIR as directed by physician.

**Supplied:** In bottles of 100 white, scored tablets. Each tablet contains: glyceryl guaiacolate 100 mg.; ephedrine sulfate 24 mg.; theophylline 100 mg.; phenobarbital 8 mg.; thenyldiamine HCl 10 mg.

**References:** 1. Spielman, A. D.: Ann. Allergy **18**:281, 1960. 2. Waldbott, G. L.: in press. 3. Schwartz, E. et al: Am. Pract. & Digest Treat. **7**:585, 1956. 4. Ogden, H. D. and Fuchs, M.: J. Louisiana M. Soc. **111**:175, 1959. 5. Perry, W. F. and Boyd, E. M.: J. Pharmacol. & Exper. Therap. **73**:75, 1941. 6. Hayes, E. W. and Jacobs, L. S.: Dis. Chest **30**:441, 1956.

BREON

Rx PRODUCTS DIVISION
Breon Laboratories Inc. • New York 18, N. Y.

## In summer respiratory allergies,

the treatment problem is to relieve congestion. Valuable as antihistamines are against sneezing, itchy, weeping eyes and rhinorrhea, they are less effective against nasal congestion.[1]

# NOVAHISTINE®
# DECONGESTS

Novahistine provides more than simple antihistaminic effect. It shrinks congested mucous membranes (nasal, pharyngeal, laryngeal, conjunctival), opens up air passages, promotes sinus drainage, and helps prevent mouth breathing.

### NOVAHISTINE LP TABLETS

8 to 12 hour relief with a single adult dose of 2 tablets. Each tablet contains 25 mg. phenylephrine HCl (a vasoconstrictor that does not increase pulse rate) and 4 mg. chlorprophenpyridamine maleate (a potent, well-tolerated antihistamine).

### NOVAHISTINE ELIXIR

exceptionally palatable liquid that children like to take. Each 5 ml. teaspoonful contains 5 mg. phenylephrine HCl and 2 mg. chlorprophenpyridamine maleate.

1. Beckman, H.: *Pharmacology: The Nature, Action and Use of Drugs*, 2nd Ed. W. B. Saunders Company, Philadelphia and London, 1961, p. 673.

PITMAN-MOORE COMPANY
Division of The Dow Chemical Company
Indianapolis 6, Indiana

# Postgraduate Medicine

OFFICIAL JOURNAL OF THE INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION



*Editor-in-Chief*
CHARLES W. MAYO, M.D.
*Rochester, Minn.*

*Contributing Editor*
MORRIS FISHBEIN, M.D.
*Chicago, Ill.*

*Executive Editor*
SYLVIA COVET
*Minneapolis, Minn.*

## EDITORIAL ADVISORY BOARDS

### MEDICAL

John F. Briggs, M.D.
ST. PAUL, MINN.

Ray F. Farquharson, M.B.
TORONTO, ONT.

William T. Foulk, M.D.
ROCHESTER, MINN.

J. Roscoe Miller, M.D.
CHICAGO, ILL.

H. Marvin Pollard, M.D.
ANN ARBOR, MICH.

Dwight L. Wilbur, M.D.
SAN FRANCISCO, CALIF.

### SURGICAL

Richard B. Cattell, M.D.
BOSTON, MASS.

George W. Crile, Jr., M.D.
CLEVELAND, OHIO

Michael E. DeBakey, M.D.
HOUSTON, TEX.

Howard A. Patterson, M.D.
NEW YORK, N.Y.

Francois Roy, M.D.
QUEBEC, QUE.

I. Ridgeway Trimble, M.D.
BALTIMORE, MD.

### CLINICOPATHOLOGIC CONFERENCES

William J. Donnelly, M.D.
CHICAGO, ILL.

William J. Gillesby, M.D.
CHICAGO, ILL.

Charles B. Puestow, M.D.
CHICAGO, ILL.

### FORENSIC MEDICINE

Oliver C. Schroeder, Jr., LL.B.
CLEVELAND, OHIO

Milton Helpern, M.D.
NEW YORK, N.Y.

Samuel A. Levinson, M.D.
CHICAGO, ILL.

### LABORATORY MEDICINE

Ellis S. Benson, M.D.
MINNEAPOLIS, MINN.

### RADIOLOGY

Paul C. Hodges, M.D.
CHICAGO, ILL.

### NUTRITION

Jean Mayer, PH.D.
BOSTON, MASS.

## SPECIALTY ADVISORY BOARD

| | | |
|---|---|---|
| Brian Blades, M.D. | *Thoracic Surgery* | WASHINGTON, D.C. |
| J. Barrett Brown, M.D. | *Plastic Surgery* | ST. LOUIS, MO. |
| R. Lee Clark, Jr., M.D. | *Cancer Research* | HOUSTON, TEX. |
| James L. Dennis, M.D. | *Pediatrics* | OAKLAND, CALIF. |
| Franklin G. Ebaugh, M.D. | *Psychiatry* | DENVER, COLO. |
| Edmund B. Flink, M.D. | *Endocrinology* | MORGANTOWN, W. VA. |
| Walter Freeman, M.D. | *Neurology* | LOS ALTOS, CALIF. |
| George W. Hyatt, M.D. | *Orthopedics* | WASHINGTON, D.C. |
| S. Leon Israel, M.D. | *Obstetrics & Gynecology* | PHILADELPHIA, PA. |
| Sture A. M. Johnson, M.D. | *Dermatology & Syphilology* | MADISON, WIS. |
| Julius Lempert, M.D. | *Otology* | NEW YORK, N.Y. |
| Charles F. McCuskey, M.D. | *Anesthesiology* | LOS ANGELES, CALIF. |
| Edward B. D. Neuhauser, M.D. | *Radiology* | BOSTON, MASS. |
| Theodore Rasmussen, M.D. | *Neurologic Surgery* | MONTREAL, QUE. |
| Hamilton B. G. Robinson, D.D.S. | *Dentistry* | KANSAS CITY, MO. |
| Harry L. Rogers, M.D. | *Allergy* | PHILADELPHIA, PA. |
| Stuart T. Ross, M.D. | *Proctology* | GARDEN CITY, N.Y. |
| Howard A. Rusk, M.D. | *Rehabilitation* | NEW YORK, N.Y. |
| William H. Saunders, M.D. | *Otolaryngology* | COLUMBUS, OHIO |
| Arthur Purdy Stout, M.D. | *Pathology* | NEW YORK, N.Y. |
| Gilbert J. Thomas, M.D. | *Urology* | LOS ANGELES, CALIF. |
| Jan H. Tillisch, M.D. | *Aviation Medicine* | ROCHESTER, MINN. |
| Derrick Vail, M.D. | *Ophthalmology* | CHICAGO, ILL. |

### GREAT BRITAIN

E. R. Cullinan, F.R.C.P.
LONDON

C. Naunton Morgan, F.R.C.S.
LONDON

R. Guy Pulvertaft, F.R.C.S.
DERBY

### AUSTRALIA

Kenneth W. Starr, F.R.C.S.
SYDNEY

# Problems and Solutions

Readers are invited to submit questions relating to problem cases. Inquiries will be answered by qualified consultants and replies forwarded by mail immediately. Selected problems and solutions are published each month in this section.

## • PHENYLKETONURIA

**P.** Is it possible to prevent or to cure phenylketonuria? What is our present state of knowledge concerning this condition? If a cure is possible and if amentia can be prevented by early diagnosis, what screening test should be used?

M.D.—Ontario

**S.** Phenylketonuria represents a genetic, recessive biochemical abnormality that results in the failure of phenylalanine to oxidize to tyrosine (caused by a deficiency in the liver enzyme phenylalanine hydroxylase). Under such circumstances there is a cumulative build-up of phenylalanine in body fluids. This excess is partially metabolized to phenylketone bodies (phenylpyruvate, acetate, lactate and acetylglutamide), and these are excreted in the urine.

The persistence of high serum concentrations of phenylalanine is associated with mental deficiency, although the exact mechanism of injury to the central nervous system is not understood. About 90 per cent of affected children are blue-eyed and blond, which reflects their inability to produce the tyrosine necessary for melanin pigments. About one-third of affected children also have eczematous conditions. Urine and body odors are accurately described as "mousy."

In the presence of well-developed phenylketonuria, the ferric chloride "diaper" test will give strongly positive results. Unfortunately, this is not true during the first week of life, and in some instances the test will not give positive results until the sixth or seventh week of life. The serum phenylalanine level is greater than 15 mg. per 100 ml. before phenylpyruvic acid appears in the urine; once such levels are attained, brain damage begins, although it may not be maximal for as long as three years. A low-phenylalanine diet constitutes the only therapy for this condition. It is important to realize, however, that such treatment may only arrest the progress of brain damage; it cannot reverse damage already done to the brain. Nevertheless, early diagnosis and early diet therapy hold a hopeful prognosis. Even the older child with severe brain damage shows improved behavior after adequate dietary control has been established.

All infants should be routinely screened with the ferric chloride test. Infants with a suggestive family history probably should be followed during early neonatal life by serial tests of serum phenylalanine levels.

## • LABOR-INDUCING DRUGS

**P.** I would like to know if quinine is still used to induce labor and if PITOCIN® or PITUITRIN® may be administered intramuscularly to stimulate labor when full dilatation has occurred.

M.D.—Arkansas

**S.** The use of quinine to induce labor was popular about 35 or 40 years ago. Quinine is no longer used as an adjunct to labor, because reports showed that it did not increase uterine contractility when the intrauterine bag technic was employed and because fetal deaths were attributed to its use.

There is no objection to the intramuscular administration of small doses (0.25 unit) of oxytocin under the condition mentioned if vaginal examination shows no contraindication (no malposition or bony disproportion) and if the physician remains in attendance. However, it generally is preferable to administer a diluted solution of oxytocin intravenously rather than intramuscularly, because quantity and speed of injection can be better regulated.

*(Continued on page A-15)*

DARICON IN BRIEF

DARICON is oxyphencyclimine hydrochloride, a long-acting, highly effective anticholinergic with potent antisecretory and antispasmodic actions. DARICON provides 24-hour relief from the pain and discomfort associated with g.i. disturbances, usually on just b.i.d. dosage.

**INDICATIONS:** DARICON is valuable for the adjunctive management of peptic ulcers—duodenal, gastric, and marginal types; functional bowel syndrome—irritable colon, spastic colon including mucous colitis; pylorospasm; chronic, nonspecific ulcerative colitis; biliary tract disease including cholecystitis and cholelithiasis; hiatus hernia accompanied by esophagitis, gastritis, or ulcer; gastritis—acute or hypertrophic; duodenitis; bladder spasm with or without cystitis; ureteral spasm, as with stones or pyelonephritis.

**SIDE EFFECTS AND PRECAUTIONS:** Certain side actions common to anticholinergic agents may occur with DARICON. Dryness of the mouth is the most common effect. Blurring of vision, constipation, and urinary hesitancy or retention occur infrequently. These effects may decrease or disappear as therapy continues, or can be minimized by adjustment of dosage. Care should be exercised in using DARICON in patients with prostatic hypertrophy, in whom urinary retention may occur. The use of DARICON as well as other anticholinergics in patients with an associated glaucoma is not recommended except with ophthalmological approval and supervision.

**ADMINISTRATION AND DOSAGE:** The average adult dosage is one 10 mg. tablet of DARICON twice daily—in the morning and at night before retiring. Due to differences in patient response, the dose should be adjusted in relation to therapeutic response. While as much as 50 mg. daily is well tolerated by some adult patients, other patients respond well to 5 mg. daily.

**SUPPLIED:** DARICON Tablets, 10 mg. of oxyphencyclimine HCl. In prescription size bottles of 60 white, scored tablets.

**CAUTION:** Federal law prohibits dispensing without prescription.

*More detailed professional information available on request.*




**• ANGINA**

**P.** During a recent trip to Denver, a man who always has lived at sea level experienced a sudden burning sensation in the substernal region after walking several blocks in a 20° F. temperature. The pain became so uncomfortable that he had to rest. After sitting awhile, the burning sensation disappeared, but a dull ache persisted for about an hour.

The following day his chest still burned and ached on exertion. There was no giddiness, syncope, coughing or evidence of infection. The aching ceased within a few days after he returned to his home in Memphis.

Can high altitudes cause anginalike pain or soreness and inflammation?

M.D.—Tennessee

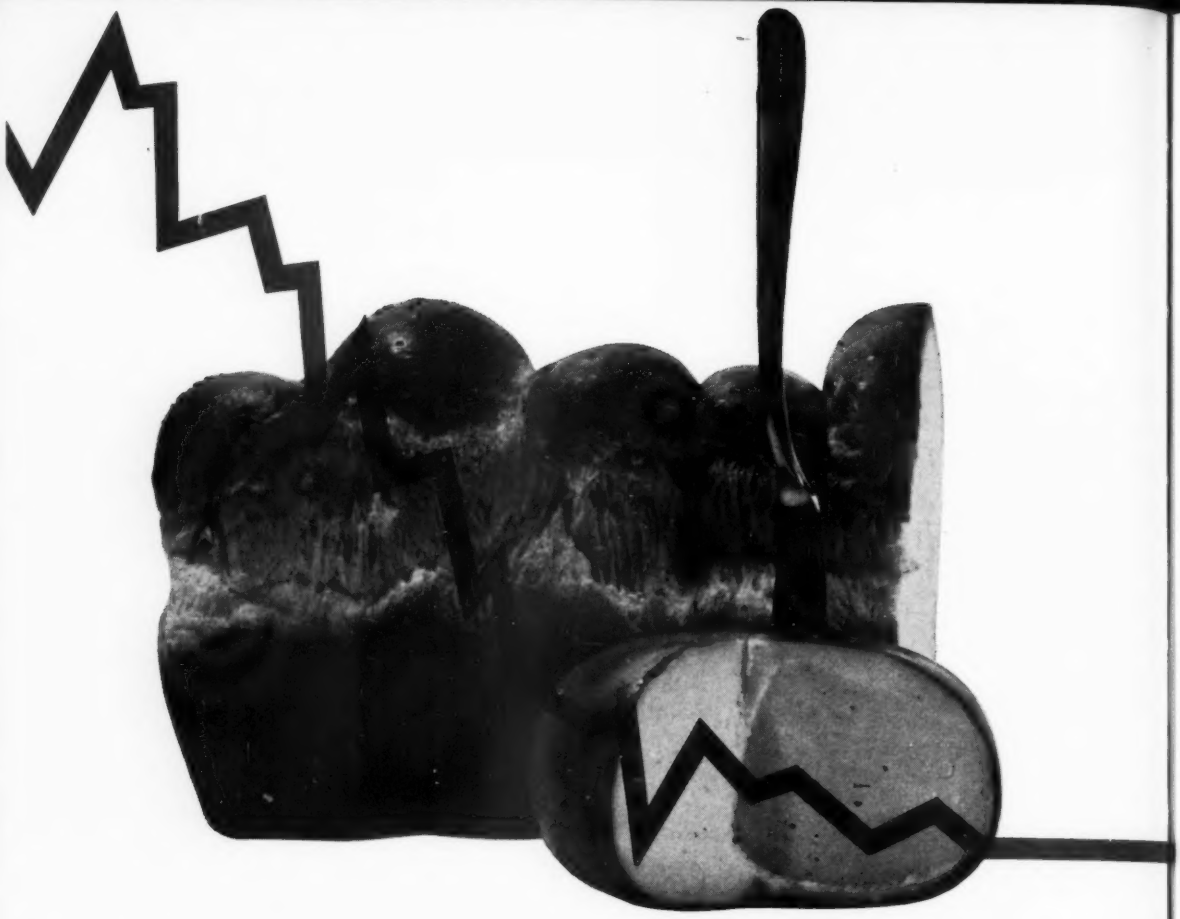
**S.** Anginal attacks are often precipitated by exertion in high altitudes and cold weather. In the case described, a detailed history, physical examination and appropriate laboratory tests are indicated to evaluate the pain.

**• BREECH PRESENTATION**

**P.** A Gravida III was to have a tubal ligation after delivery for economic reasons. The patient had a breech presentation. Since in vaginal delivery the fetal morbidity and mortality are considerably greater in breech presentation than in cephalic presentation, there was a question as to whether or not the patient should be delivered by cesarean section. In breech presentation is the fetal morbidity less with cesarean section than with vaginal delivery? Since this patient's abdomen had to be opened in any case and since she would have no further pregnancies, would the section have been the better procedure?

M.D.—Kentucky

**S.** The fetal mortality is higher in breech presentation with full-term vaginal delivery because of asphyxia and intracranial hemorrhage. It may be minimized by careful observation of the patient, pelvioradiography during labor, and vaginal examination to estimate pelvic capacity. The morbidity from cesarean section is higher than the morbidity from tubal ligation performed immediately post partum. Cesarean section should not be done except for obstetric indications; tubal ligation is not an indication for cesarean section.



**Adding Orinase may improve control significantly in diabetics now imperfectly managed on diet alone.**[1-4]

Orinase releases native insulin via physiologic channels, giving the patient direct metabolic support. And Orinase dosage is flexible and readily individualized.

To improve control in many diabetics on dietotherapy — add Orinase. It can make a gratifying clinical difference.

*Indications:* Orinase is indicated as the therapeutic agent of choice in the majority of selected cases of adult or maturity-onset type of diabetes mellitus. In certain patients with labile diabetes, the use of Orinase as a supplement to insulin therapy may effect stabilization of the diabetic condition and lower insulin requirement.

*Dosage:*

Patients not receiving insulin — There is no fixed regimen for initiating Orinase therapy, but a suggested method is:

**First day** — 6 Orinase tablets (3.0 Gm.). **Second day** — 4 Orinase tablets (2.0 Gm.). **Third day** — 2 Orinase tablets (1.0 Gm.). **Fourth and subsequent days** — 2 Orinase tablets (1.0 Gm.) with increase or decrease as necessary to control glycosuria.

There is no fixed maintenance dose of Orinase; therapy may be individualized according to patient response. Adjust the maintenance dose (usually 1 to 4 tablets) to the smallest dose consistent with good control. The daily maintenance dose may be given once daily or in divided doses.

Patients receiving insulin (less than 20 units) — discontinue insulin and institute Orinase; (20 to 40 units) — initiate Orinase with a concurrent 30 to 50% reduction in insulin dose with a further careful reduction as response to Orinase is observed; (more than 40 units) — reduce insulin by 20% and initiate Orinase with a further careful reduction in insulin dosage as response to Orinase is observed.

*Cautions:* Observe all standard diabetes precautions: dietary restriction, weight control, exercise, hygiene, avoidance of infection, and adherence to dosage. As with exogenous insulin, changes in dosage may be necessary during the course of management. In the event of stress conditions, trauma or infection, increased dosage or supplementary animal insulin may be required.

*Contraindications:* Orinase as the sole therapeutic agent is contraindicated in juvenile diabetes; unstable or brittle diabetes; and diabetes complicated by ketosis, acidosis or coma.

*Side effects:* Side effects are mild, transient and limited to approximately 3% of patients. Hypoglycemia and toxic reactions are extremely rare. Hypoglycemia is most likely to occur during the period of transition from insulin to Orinase. Other untoward reactions to Orinase are usually not of a serious nature and consist principally of gastrointestinal disturbances, headache, and variable allergic skin manifestations. The gastrointestinal disturbances (nausea, epigastric fullness, heartburn) and headache appear to be related to the size of the dose, and they frequently disappear when dosage is reduced to maintenance levels or the total daily dose is administered in divided portions after meals. The allergic skin manifestations (pruritus, erythema, and urticarial, morbilliform, or maculopapular eruptions) are transient reactions, which frequently disappear with continued drug administration. However, if the skin reactions persist, Orinase should be discontinued.

*Clinical toxicity:* Orinase appears to be remarkably free from gross clinical toxicity on the basis of experience accumulated during more than four years of clinical use. Crystalluria or other untoward effects on renal function have not been observed. Long term studies of hepatic function in humans and experience in over 600,000 diabetics have shown Orinase to be remarkably free of hepatic toxicity. There has been reported only one case of cholestatic jaundice related to Orinase administration, which occurred in a patient with pre-existing liver disease and which rapidly reversed upon discontinuance of the drug.

Each tablet contains:

Tolbutamide ..... 0.5 Gm.

Supplied in bottles of 50.

*References:*

**1.** Bollinger, R. E., *et al.*: J. Kansas M. Soc. *61*:135 (March) 1960. **2.** Williams, R. H.: Diabetes, New York, Paul B. Hoeber, Inc., 1960, pp. 491, 492. **3.** Bradley, R. F.: Ann. New York Acad. Sc. *82*:513 (Sept. 25) 1959. **4.** Sherry, S., *et al.*: Ann. New York Acad. Sc. *71*:249 (July 10) 1957.

# Orinase*

An exclusive methyl "governor" minimizes hypoglycemia.

The Upjohn Company, Kalamazoo, Michigan

*Trademark, Reg. U. S. Pat. Off. — tolbutamide, Upjohn

Copyright 1961, The Upjohn Company

# *Ready Soon — From Saunders*

## Fluhmann — The Cervix Uteri and its Diseases

### NEW! the definitive work on managing cervical disorders

Here is a new and highly authoritative presentation devoted to the cervix uteri and its diseases. Special attention has been directed to diagnosis, clinical manifestations, and both medical and surgical treatment. A richly illustrated section of *Anatomy* emphasizes clinical applications of anatomic, embryologic and physiologic detail. Diagnostic procedures are illustrated and meticulously described. Dr. Fluhmann explains techniques of office examinations, cytologic study, analysis of cervical secretions, the Schiller Test, tissue biopsies, colposcopy and roentgenographic study. Coverage of carcinoma in situ and of invasive carcinoma is exhaustive. You'll find surgical treatment described and illustrated in precise detail. Criteria for making a choice between radiation and surgical management is analyzed from every point of view. The final section of *The Cervix During Pregnancy* discusses the Incompetent Cervix, Malignant Lesions during Pregnancy, Traumatic Lesions, etc. The author's experience and wide research assure the authority of this new volume.

By C. Frederic Fluhmann, B.A., M.D., C.M., Chief of Obstetrics and Gynecology, Presbyterian Medical Center, San Francisco, California; Clinical Professor of Obstetrics and Gynecology, Stanford University School of Medicine, Palo Alto, California. 556 pages, 6⅝" x 10", with 447 illustrations. About $12.50.

*New—Just Ready!*

## Tenney and Little — Clinical Obstetrics

### NEW! A survey of recent advances and a review of persistent problems

The two authors of this book clearly discuss 24 topics of current great interest or controversy in the clinical practice of obstetrics. These are the problems which cause difficulties in the safe delivery of mother and child. Drs. Tenney and Little define sharply the present points of view at the Boston City Hospital and the Boston Lying-in Hospital. Their massive experience is brought to bear on such timely problems as—*Obstetrical Management of Rhesus Factor and ABO Incompatability—Management of Third Trimester Bleeding (Safety or Economy)—Induction of Labor: Methods and Indications—Cecarean Section: Hazardous or Panacea?* All the advances discussed have proved their clinical value.

By Benjamin Tenney, M.D., Director of Obstetrics and Gynecology, Boston City Hospital; Clinical Professor of Obstetrics, Harvard Medical School; and Brian Little, M.D., Boston Lying-in Hospital; Associate in Obstetrics, Harvard Medical School. About 480 pages, 6½" x 9¾", illustrated. About $9.00.

*New—Ready September!*

## Blechschmidt — The Stages of Human Development Before Birth

### NEW!

Graphically depicting all the intricacies of prenatal growth and development, this beautifully illustrated new atlas gives you sound visual guidance on complicated embryological relationships. It will greatly aid you in understanding the problems of the mother and in managing complications during pregnancy. Detailed coverage ranges from the time of conception until the moment of birth. Great pains have been taken by the author to make this distinguished volume a pictorial masterpiece. Complete reconstructions of early stages are included with rare microscopical preparations and histological sections of unusually fine detail. All illustrations are on an enlarged scale. Logically organized to show the development of the embryo by body regions, it provides you with valuable insight into the early functioning of human organs. Chapter divisions are made on this same topographical basis. The material is arranged in an exceptionally easy-to-use format—with illustrations on the right hand pages, and accompanying text on the left. The text is run bilingually in two columns—one German and one English.

By E. Blechschmidt, M.D., Professor of Anatomy and Director of the Institute of Anatomy, University of Gottingen, Germany. About 630 pages, 7" x 10", with about 600 illustrations. About $23.00.

*New—Just Ready!*

**ORDER TODAY!**

PGM 8-61

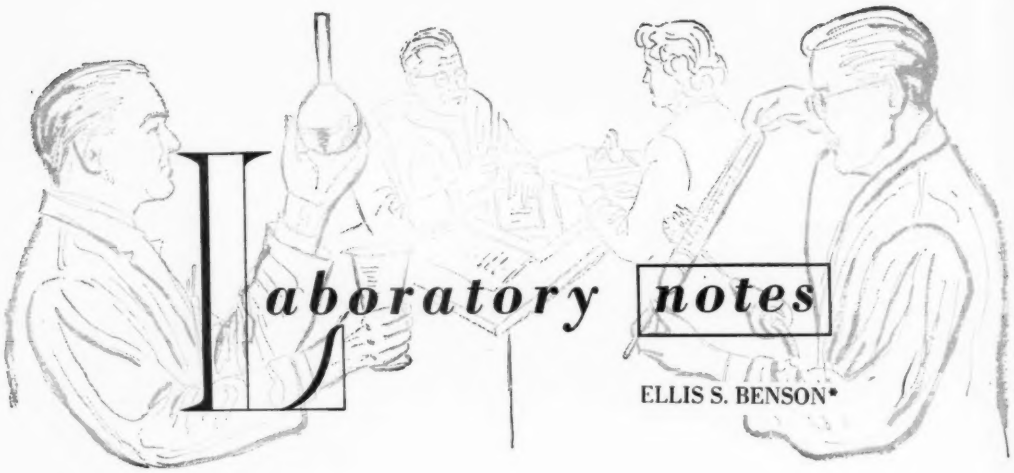
W. B. **SAUNDERS** Company, West Washington Square, Philadelphia 5

Please send and charge my account: ☐ Easy Pay Plan ($5 per mo.)

☐ *Fluhmann—The Cervix Uteri* ..... *About $12.50*
☐ *Tenney and Little—Clinical Obstetrics* ..... *About $ 9.00*
☐ *Blechschmidt—Stages of Human Development before Birth* ..... *About $23.00*

Name _____

Address _____



# Laboratory notes

ELLIS S. BENSON*

## Current Status of Tests of Adrenocortical Function, Part 2

JAMES C. MELBY†

*University of Arkansas School of Medicine, Little Rock*

### *Classification of Adrenocortical Hypofunction*

PRIMARY *adrenocortical insufficiency* (*panhypocorticalism*)—Acute—A provisional diagnosis of acute adrenocortical failure or addisonian crisis requires that treatment be instituted without delay. Confirmation by a corticotropin (ACTH)-response test should be postponed until recovery is obtained. The presence of pigmentation, hyponatremia, hyperkalemia and azotemia in a patient with peripheral circulatory failure is strongly suggestive of Addison's disease; however, the identical clinical picture may occur in salt-losing nephritis. Failure of the patient to conserve administered sodium while receiving adequate replacement of adrenal steroid hormones suggests a primary renal lesion.

Since the original reports of Waterhouse[1] and Friderichsen,[2] peripheral vascular collapse due to septicemia has been attributed to secretory failure of the adrenals. To date, permanent adrenal insufficiency has not been noted in those patients who have survived the Waterhouse-Friderichsen syndrome. Spink and I[3] reported on the concentrations of cortisol in the plasma of 22 patients with shock due to infection, and all values were higher than basal levels measured in healthy subjects. In six patients tested, there was a rise in plasma cortisol following administration of ACTH. The therapeutic effects of administered cortisol in these cases cannot be regarded as due to replacement, because the required doses of the steroid hormones greatly exceeded the maximal secretory capacity of the adrenal cortex. It is probable that acute adrenal insufficiency is not a feature of the Waterhouse-Friderichsen syndrome.

Chronic (Addison's disease)—Addison's disease is now being diagnosed more frequently than formerly. This increased recognition is due in part to the availability of specific tests of adrenocortical function. In addition, the entity of partial adrenal insufficiency has been recognized, in which a remnant of functioning adrenal cortex is continuously stimulated by endogenous ACTH to produce a normal basal steroid output. When an infusion of ACTH is given, however, no rise

*(Continued on page A-20)*

*Director of Hospital Laboratories and Associate Professor of Clinical Medicine and of Pathology, University of Minnesota Medical School, Minneapolis, Minnesota.

†Associate Professor of Medicine and Biochemistry, University of Arkansas School of Medicine, Little Rock, Arkansas.

# FOUR HUNDRED MILLIGRAMS OF PURE

# PAIN RELIEF

## NEW analexin®-400

400 milligrams of phenyramidol HCl

## THE ONLY SIGNIFICANT RESPONSE IS RELIEF FROM PAIN

**EXCEEDINGLY EFFECTIVE** "... The 85.1% incidence of effectiveness with the 400 mg. dose has exceeded the analgesic effectiveness of any other analgesic agent which we have studied to date, either alone or in combination....The utilization of higher doses for short periods of time indicates that the medication has a large therapeutic range, and this is reflected in the high incidence of effectiveness and low likelihood of untoward reactions.

"The practicing physician translating this into his own needs may be completely confident of using a medication with an excellent predictability and a safe analgesic response."[1]

**EXTRAORDINARY MARGIN OF SAFETY.** *Analexin-400 is non-narcotic and not narcotic related;* thus, it presents no danger of habituation or any other reaction associated with the frequent use of narcotics. Nor will Analexin-400 produce sedation, mental confusion or depression occasionally observed with other analgesics or interneuronal blocking agents.[1-23]

**INDICATIONS:** Relief of pain in injury, low back pain, premenstrual cramping, dysmenorrhea, postoperative pain, and a wide variety of recurring and acute painful conditions.

**DOSAGE:** One capsule at onset of pain, followed by 1 capsule at intervals of 1 to 4 hours, as needed.

**REFERENCES:** From the Symposium, *Recent Concepts of Pain and Analgesia*, held in the Hall of States, American Hospital Association, Chicago, February 15, 1961: 1. Batterman, R. C.: *Non-Narcotic Analgesia in Ambulatory Patients.* 2. O'Dell, T. B.: *Experimental Parameters in the Evaluation of Analgesics.* 3. Miller, L. D.: *Distribution, Excretion and Metabolic Fate of Phenyramidol.* 4. Beisler, E.: *Preliminary Report of Experience with Phenyramidol for Dental Analgesia.* 5. Bader, G.: *Preliminary Report on the Use of Analexin for Dysmenorrhea in Telephone Operators.* 6. Taylor, S. L.: *Phenyramidol in General Hospital Orthopedics.* 7. Bodi, T.: *Pain Management Among Clinic Outpatients.* 8. Ramunis, J.: *Experience of an Industrial Surgeon with Phenyramidol.* 9. Kast, E. C.: *Methodological Considerations in the Clinical Evaluation of an Analgesic.* 10. Collopy, C. T.: *Preliminary Comparisons of Two Non-Narcotic Analgesic Agents in Hospitalized Orthopedic Patients.* 11. Cass, L. J.: *Report on the Analgesic and Calmative Effectiveness of Two Preparations on Patients with Acute and Chronic Pain.* 12. Lamphier, T. A.: *Intravenous Phenyramidol in the Management of Low Back Pain and Allied Disorders.* 13. O'Dell, T. B.: Chicago Med. *63*:9, 1961. 14. Kast, E. C.: Chicago Med. *63*:17, 1961. 15. Wainer, A. S.: J. Am. M. Women's A. *16*:218, 1961. 16. Batterman, R. C.: Ann. New York Acad. Sc. *86*:203, 1960. 17. O'Dell, T. B.: Ann. New York Acad. Sc. *86*:191, 1960. 18. O'Dell, T. B., *et al.*: J. Pharmacol. & Exper. Therap. *128*:65, 1960. 19. O'Dell, T. B., *et al.*: Fed. Proc. *18*:1694, 1959. 20. Gray, A. P., *et al.*: J. Am. Chem. Soc. *81*:4347, 1959. 21. Wainer, A. S.: Clin. Med. *7*:2331, 1960. 22. Clinical data in files of Medical Dept., Irwin, Neisler & Co., 1959. 23. Batterman, R. C., *et al.*: Am. J. Med. Sc. *238*:315, 1959.

ANOTHER ACHIEVEMENT OF NEISLER RESEARCH **IRWIN, NEISLER & CO.** 75th year DECATUR, ILLINOIS

in plasma cortisol can be detected. The patient with incomplete or partial Addison's disease lacks adrenocortical reserve, and symptoms are precipitated by trauma or febrile illness; however, they may be absent or minimal without the superimposition of stress.

Adrenal insufficiency can be diagnosed reliably only by the demonstration of failure to increase blood cortisol levels or urinary 17-hydroxycorticosteroid (17-OHCS) or 17-ketogenic steroid (17-KGS) excretion in response to intravenous or intramuscular injections of ACTH. Urinary 17-ketosteroid (17-KS) excretion is unreliable as an index of adrenocortical functional capacity. A single determination of plasma cortisol or 24 hour urinary 17-OHCS or 17-KGS excretion is not useful and may be misleading in diagnosing adrenal insufficiency. The following test, standardized by Jenkins et al.,[4] is commonly used for determining urinary excretion of 17-OHCS:

Urine is collected for 24 hours on two control days and on two consecutive days, on each of which 25 I.U. of ACTH is injected intravenously over eight hours. Normal subjects excrete 1 to 10 mg. 17-OHCS per day on control days, 5 to 25 mg. on the first day of ACTH stimulation, and 15 to 41 mg. on the second day. Patients with Addison's disease fail to excrete additional 17-OHCS on days of ACTH stimulation.

Christy, Wallace and Jailer[5] simplified the testing of adrenocortical functional capacity by measuring the change in concentration of cortisol in the plasma before and after a four hour intravenous infusion of ACTH. I have used the following similar procedure for the past four years:

An intravenous infusion of 40 U.S.P. units of ACTH dissolved in 500 ml. of 5 per cent dextrose in saline is given over a period of four hours. Initially and at the conclusion of the infusion of ACTH, 15 ml. of heparinized blood is secured. The erythrocytes are separated from the plasma within 30 minutes. The plasma samples are frozen until determinations of cortisol are made. A modification of the method of Silber and Porter,[6] as described by Wu and Mason,[7] is employed for analysis. The results for eight normal subjects are shown in figure 1a. The mean control value for cortisol was 15 μg. per 100 ml. of plasma, with a range of 5 to 24 μg. per cent. Following the infusion of ACTH, the concentrations rose to a range of 32 to 63 μg. per cent, with a mean of 46 μg. per cent.

The results of ACTH tests carried out in six patients with the clinical features of Addison's disease are presented in figure 1b. It is apparent that no response to ACTH was obtained in any patient and that circulating cortisol could not be detected in three patients.

Figure 1c shows the results of ACTH tests in five patients with limited adrenal reserve or partial Addison's disease. Hyperpigmentation is not necessarily a manifestation of this condition. An interesting finding in these patients was the relatively high plasma concentrations of cortisol prior to infusion of ACTH, presumably because of maximal endogenous ACTH secretion. No response to ACTH was obtained in these patients, as was noted in patients with classic Addison's disease. This remarkable separation from the normal group has been observed repeatedly. Because of its high validity, we have adopted this test as the *sine qua non* for the diagnosis of adrenal insufficiency.

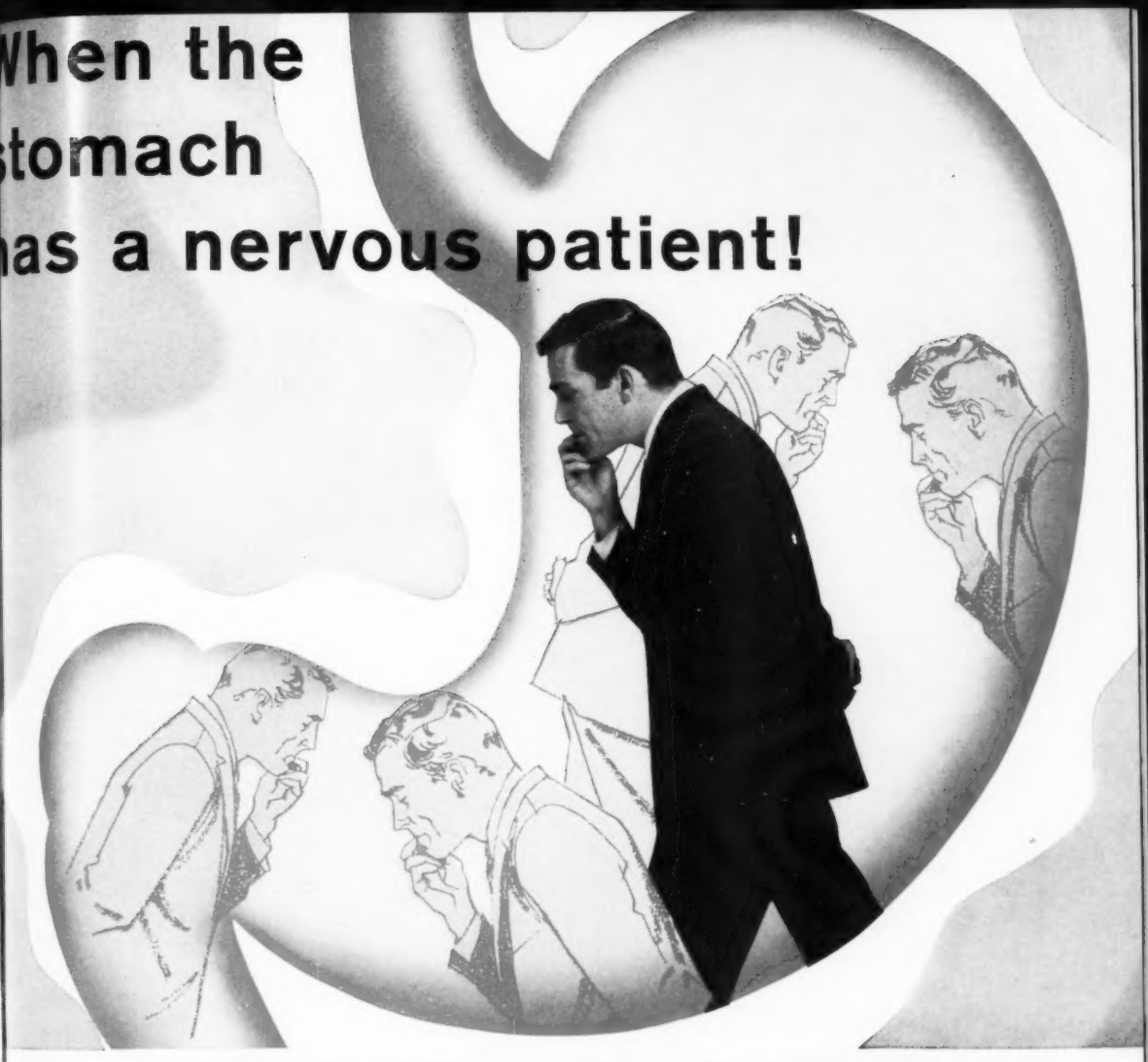
*Secondary adrenocortical insufficiency*—It should be emphasized that the manifestations of aldosterone deficiency are not ordinarily observed in panhypopituitarism. Some patients have significant hyponatremia, which may reflect water retention and dilution due to deficiency of cortisol or thyroxin, or both. The pallor of panhypopituitarism distinguishes it from classic Addison's disease.

ACTH test—The rise in plasma cortisol after intravenous infusion of ACTH is usually markedly impaired (figure 1d). There often is overlap with normal control responses, but the ACTH test ordinarily will separate primary from secondary adrenocortical insufficiency. However, in some patients with panhypopituitarism, no rise in plasma cortisol may be detected on the initial ACTH test. Repeated stimulation of the adrenal cortex with ACTH gel or corticotropin-zinc (80 units given intramuscularly for four days) restores normal responsiveness to intravenously administered ACTH (figure 1d). An ACTH test must be performed prior to or after the tests to be described.

Pyrogen test—Investigations of the effect of bacterial pyrogen on pituitary-adrenal secretory activity led to the development of a simple clinical procedure, the pyrogen test, for assessment of ACTH production in patients with panhypopituitarism and in patients who have had steroid therapy.[8,9] Blood samples for plasma cortisol determinations are obtained at 30, 60, 120, 180 and 240 minutes after an intravenous injection

*(Continued on page A-22)*

# When the stomach has a nervous patient!



# BUTIBEL®

antispasmodic/sedative

**relaxes the tense patient and his jittery stomach...without the sedative "build-up" many patients experience with phenobarbital preparations.**

BUTIBEL combines the "time-matched" components—BUTISOL SODIUM® butabarbital sodium 15 mg. and extract of belladonna 15 mg.—each having approximately 5 hours' duration of effect. Thus, with Butibel there is no overlapping sedation, no antispasmodic gap—t.i.d. dosage keeps the patient comfortable without sluggishness.

*Available as:* BUTIBEL Tablets • Elixir • Prestabs® Butibel R-A (Repeat Action Tablets)

McNEIL LABORATORIES, INC., Fort Washington, Pa.

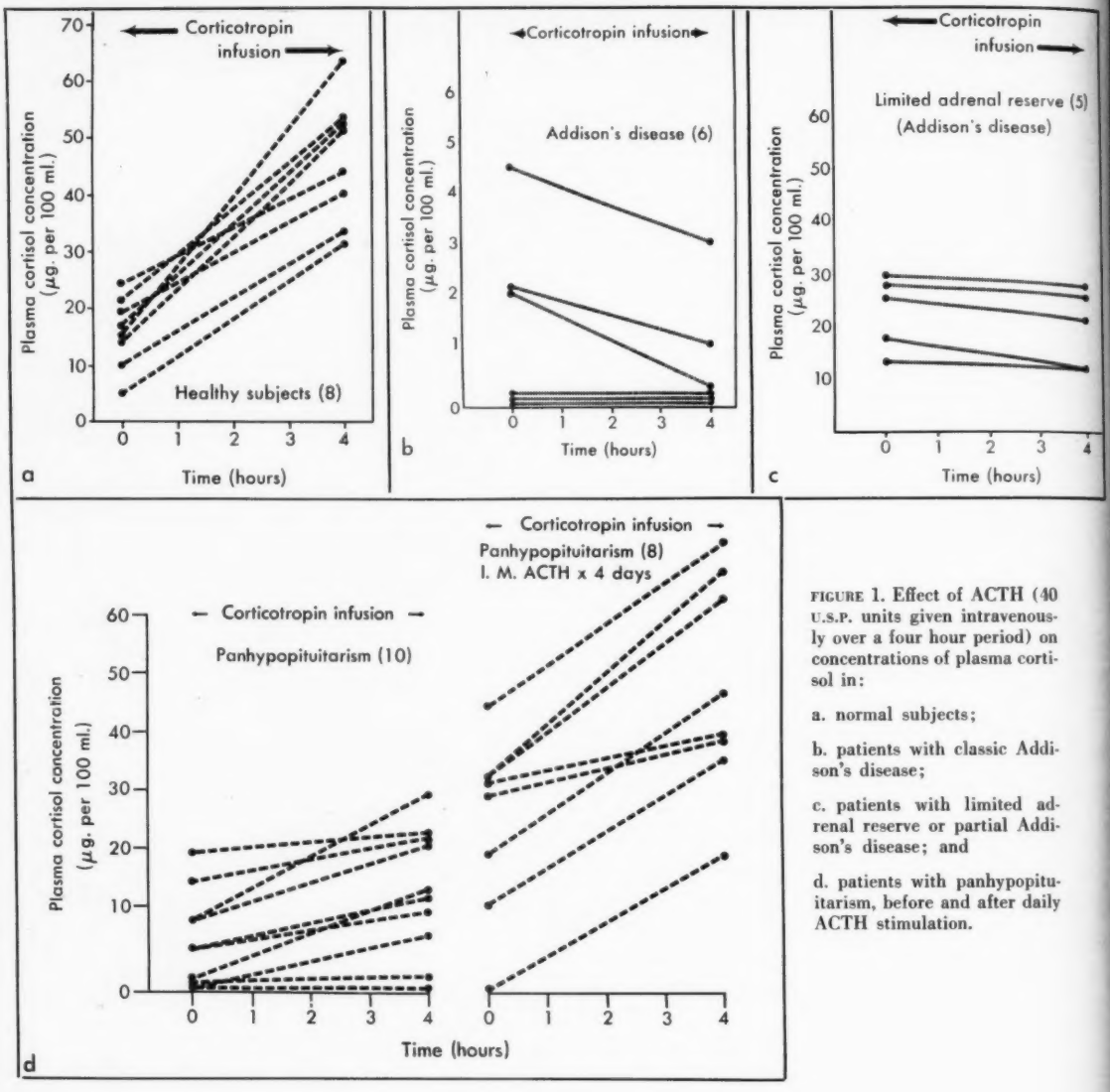



FIGURE 1. Effect of ACTH (40 U.S.P. units given intravenously over a four hour period) on concentrations of plasma cortisol in:

a. normal subjects;

b. patients with classic Addison's disease;

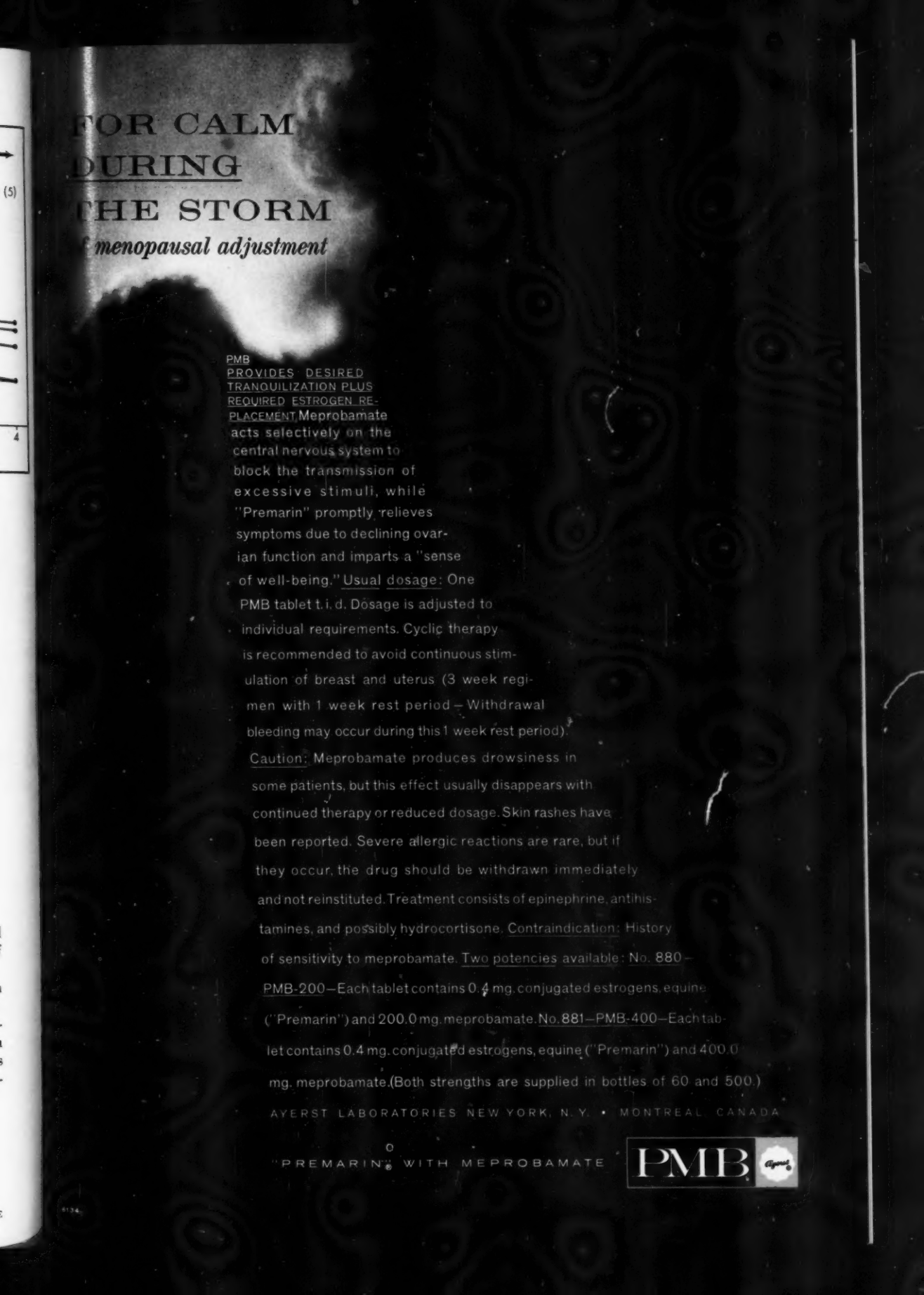
c. patients with limited adrenal reserve or partial Addison's disease; and

d. patients with panhypopituitarism, before and after daily ACTH stimulation.

of 0.25 μg. of a lipid-polysaccharide-polypeptide complex (endotoxin) derived from *Salmonella abortus equi*. In healthy subjects, an abrupt rise in plasma cortisol occurs two hours after the injection of pyrogen. No response is obtained in patients with panhypopituitarism (figure 2). Similarly, no response is obtained in patients receiving large doses of cortisol or its analogues. Pituitary-adrenal responsiveness to injected pyrogen is gradually restored to normal five months after the discontinuance of exogenous steroid therapy, independent of duration and dosage of previous steroid therapy.[10]

Su 4885 (methopyrapone) test—Interruption of the servo-mechanism (negative feedback) which regulates pituitary ACTH and adrenocortical secretory activity by a chemical inhibitor of a specific adrenal enzyme, 11-β-hydroxylase, has been utilized for the diagnosis of secondary ad-

*(Continued on page A-24)*


FOR CALM
DURING
THE STORM
menopausal adjustment
PMB
PROVIDES DESIRED
TRANQUILIZATION PLUS
REQUIRED ESTROGEN RE-
PLACEMENT. Meprobamate
acts selectively on the
central nervous system to
block the transmission of
excessive stimuli, while
"Premarin" promptly relieves
symptoms due to declining ovar-
ian function and imparts a "sense
of well-being." Usual dosage: One
PMB tablet t.i.d. Dosage is adjusted to
individual requirements. Cyclic therapy
is recommended to avoid continuous stim-
ulation of breast and uterus (3 week regi-
men with 1 week rest period – Withdrawal
bleeding may occur during this 1 week rest period).
Caution: Meprobamate produces drowsiness in
some patients, but this effect usually disappears with
continued therapy or reduced dosage. Skin rashes have
been reported. Severe allergic reactions are rare, but if
they occur, the drug should be withdrawn immediately
and not reinstituted. Treatment consists of epinephrine, antihis-
tamines, and possibly hydrocortisone. Contraindication: History
of sensitivity to meprobamate. Two potencies available: No. 880 –
PMB-200 – Each tablet contains 0.4 mg. conjugated estrogens, equine
("Premarin") and 200.0 mg. meprobamate. No. 881 – PMB-400 – Each tab-
let contains 0.4 mg. conjugated estrogens, equine ("Premarin") and 400.0
mg. meprobamate. (Both strengths are supplied in bottles of 60 and 500.)
AYERST LABORATORIES NEW YORK, N.Y. • MONTREAL, CANADA
"PREMARIN" WITH MEPROBAMATE
PMB
Ayerst

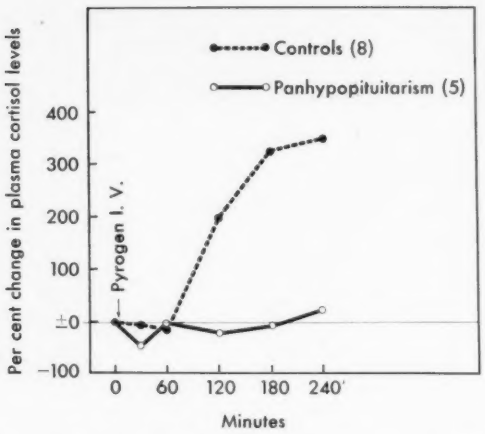



FIGURE 2. Effect of 0.25 μg. of pyrogen (Lipexal) on plasma cortisol concentrations in healthy subjects and in patients with panhypopituitarism.

renocortical insufficiency. Su 4885, a relatively nontoxic agent developed from DDT-like cytotoxins, blocks the final step in the biosynthesis of cortisol: 11-deoxycortisol → cortisol.

When the production of cortisol diminishes, the pituitary, signaled by the midbrain, accelerates ACTH secretion. The high concentration of ACTH, in turn, stimulates the formation of more and more 11-deoxycortisol (compound S), which cannot be converted to cortisol due to the action of Su 4885. The precursor 11-deoxycortisol and its urinary metabolites (tetrahydro-11-deoxycortisol and allotetrahydro-11-deoxycortisol) give a positive reaction to the Porter-Silber reagent; thus, both plasma and urinary 17-OHCS excretions rise, indicating normal pituitary secretion of ACTH.

Liddle et al.[11] standardized the Su 4885 test by collecting urine for 17-OHCS determinations two days prior to, during, and one day after the oral administration of 500 mg. Su 4885 every four hours for six doses. Maximal rise in urinary 17-OHCS excretion occurs the day following administration of Su 4885. No rise in 17-OHCS excretion is observed in patients with panhypopituitarism. Su 4885 as the bitartrate may be given intravenously over a four hour period in a dose of 30 mg. per kilogram of body weight, and a 24 hour urine collection made. Failure to increase 17-OHCS excretion on the day of the test reflects inadequate ACTH production.

I compared the Su 4885 and pyrogen tests and found that both yielded similar results in patients with panhypopituitarism. However, a few patients with chromophobe adenomas which had been irradiated, acromegaly, and primary hypothyroidism had normal results of pyrogen tests and failed to respond to Su 4885. In patients with hypothyroidism, it was possible to obtain a normal increase in urinary 17-OHCS excretion if the dosage of Su 4885 was increased and continued for two days. It is possible that hypothalamic-pituitary-adrenal activation after pyrogen stress is not the same as activation stimulated by reduced cortisol production.

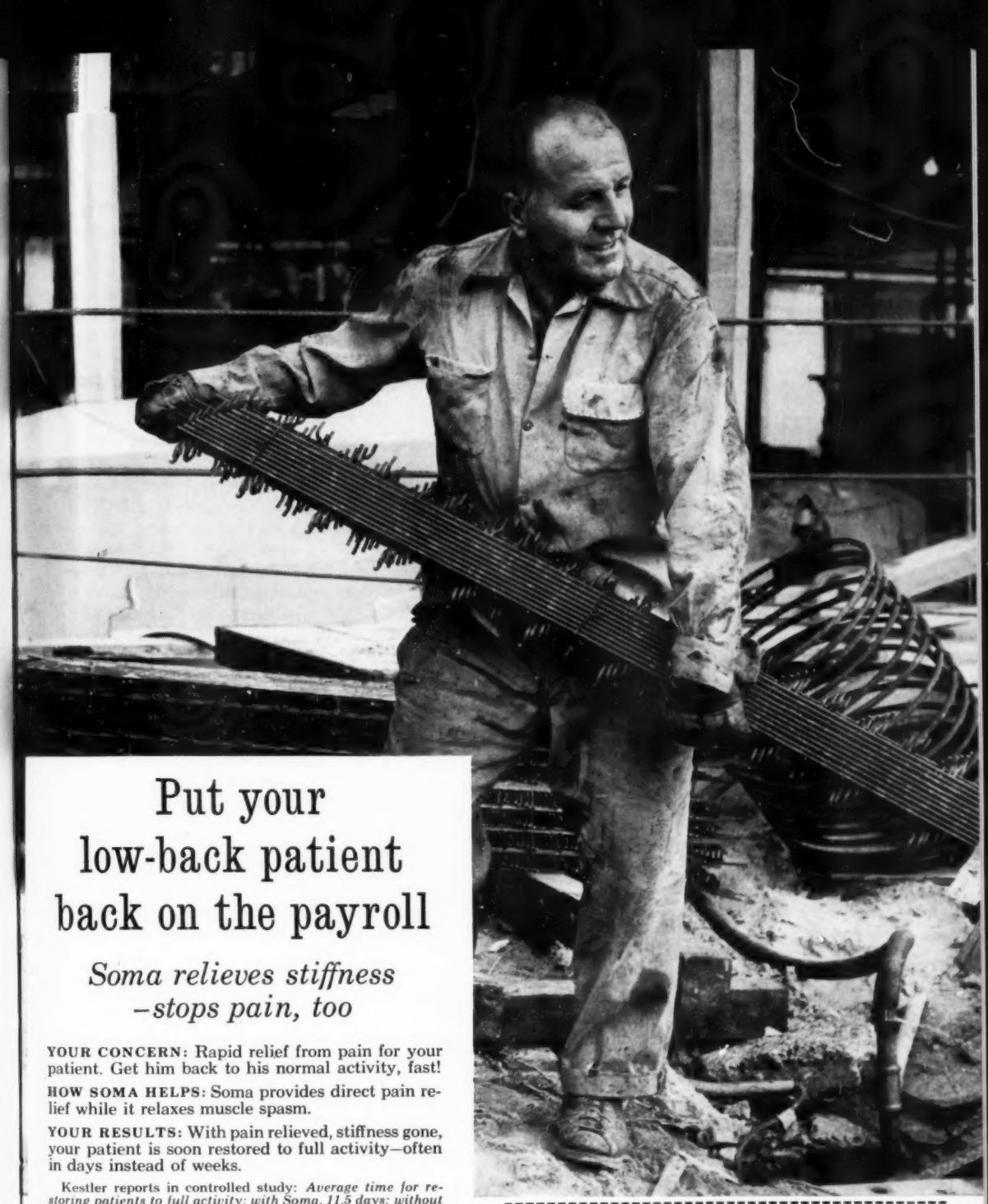
### *Classification of Adrenocortical Hyperfunction*

*Cushing's syndrome of cortisol excess*—The diagnosis of Cushing's syndrome due to either hyperplasia or tumor of the adrenal cortex can be confirmed only when urinary excretion of 17-OHCS is clearly elevated (more than 12 mg. in 24 hours). Excretion of 17-KGS correspondingly reflects excessive production of cortisol. When virilization is prominent, as in the mixed picture, 17-KS excretion will be elevated, but in pure Cushing's syndrome, measurement of 17-KS excretion usually is not helpful. It is emphasized that 17-OHCS excretion may fluctuate considerably; thus, repeated urinary specimens should be examined if clinical findings warrant this attention.[12] Frequently, in patients with the clinical manifestations of Cushing's syndrome, urinary 17-OHCS excretion may just exceed the normal range. This dilemma is compounded if the precision of the method used for measuring 17-OHCS excretion is not the best possible.

Hyperresponsiveness to ACTH in terms of blood cortisol levels and urinary 17-OHCS excretion is commonly but not invariably present. Furthermore, the hyperresponse to ACTH may be elicited in patients with tumors of the adrenal cortex, and it cannot be relied on to distinguish hyperplasia from tumor. Corroborative evidence may be obtained by the following procedures:

Diurnal variation of cortisol levels—It has not been possible to demonstrate the normal diurnal rhythm of plasma cortisol concentrations in patients with Cushing's syndrome.[13] Blood specimens should be obtained at 8 A.M. and 8 P.M. In healthy subjects and hospitalized patients with non-endocrine disease, the plasma cortisol level varies from 8 to 30 μg. per 100 ml. at 8 A.M.; it regularly declines (usually more than 50 per cent) throughout the day, so that it may not be

*(Continued on page A-26)*



# Put your low-back patient back on the payroll

*Soma relieves stiffness –stops pain, too*

**YOUR CONCERN:** Rapid relief from pain for your patient. Get him back to his normal activity, fast!

**HOW SOMA HELPS:** Soma provides direct pain relief while it relaxes muscle spasm.

**YOUR RESULTS:** With pain relieved, stiffness gone, your patient is soon restored to full activity—often in days instead of weeks.

Kestler reports in controlled study: *Average time for restoring patients to full activity: with Soma, 11.5 days; without Soma, 41 days. (J.A.M.A. Vol. 172, No. 18, April 30, 1960.)*

Soma is notably safe. Side effects are rare. Drowsiness may occur, but usually only in higher dosages. Soma is available in 350 mg. tablets. **USUAL DOSAGE:** 1 **TABLET Q.I.D.**

*The muscle relaxant with an independent pain-relieving action*

**SOMA®**

*(carisoprodol, Wallace)*

®Wallace Laboratories, Cranbury, New Jersey

Dept. S-10, Professional Services Dept.
Wallace Laboratories, Cranbury, N. J.

Gentlemen: *Please send me a physician's sample of Soma.*

Dr._____

Street_____

City_____ Zone___ State_____

Type of practice_____

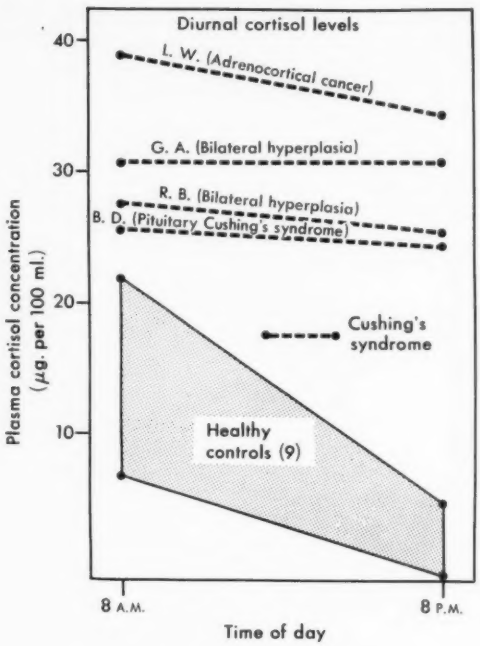



FIGURE 3. Plasma cortisol values at 8 A.M. and 8 P.M. in healthy subjects and in patients with Cushing's syndrome.

measurable from 8 P.M. to midnight. Patients with Cushing's syndrome may have high-normal or elevated plasma cortisol values at 8 A.M., with very little, if any, reduction in the evening (figure 3). The importance of this phenomenon cannot be overemphasized, as it explains the appearance of florid Cushing's syndrome in an individual whose total cortisol production is only moderately increased.

Urinary free cortisol—Extraction of urine without prior hydrolysis, chromatography in a single solvent system (chloroform: formamide), and elution and quantitation of cortisol by the Porter-Silber reaction permit estimation of free cortisol in urine. Simple extraction and the Porter-Silber reaction should suffice, however. A 24 hour urine collection should be made prior to and on the day of an eight hour infusion of 25 units of ACTH in a liter of saline. Healthy subjects excrete less than 50 μg. of cortisol on the day of the ACTH infusion. Ross[14] reported that patients with Cushing's syndrome excreted more than 50 μg. of free cortisol on the control day and more than 300 μg. on the day of the ACTH infusion. The excretion of free cortisol in urine reflects the plasma level of cortisol. Demonstrating an absence of diurnal variation in plasma cortisol is simpler and no more equivocal than using ACTH stimulation tests.

Pituitary-adrenal suppression tests—In subjects who do not have adrenal dysfunction, urinary 17-OHCS excretion may be suppressed to less than 2.0 mg. in 24 hours on the second day of oral administration of dexamethasone or fluoroprednisolone, synthetic cortisol analogues, in a dosage of 0.5 mg. every six hours for eight doses.[15] Most patients with Cushing's syndrome continue to excrete excessive amounts of 17-OHCS in urine while receiving this dosage of the potent cortisol analogues. We recently observed a patient with polyglandular adenomas and the features of Cushing's syndrome in whom urinary 17-OHCS excretion was reduced on this schedule. A dosage of 8.0 mg. or more per day of these potent cortisol analogues will suppress urinary 17-OHCS output in patients with Cushing's syndrome due to bilateral adrenocortical hyperplasia. This effect is not observed when the condition is due to tumor.

In summary, when elevated amounts of 17-OHCS are excreted in the urine of a patient with the clinical manifestations of Cushing's syndrome, the diagnosis is confirmed. It is generally agreed that no present test invariably differentiates between hyperplasia and tumor, although suppression tests are most often correct.

Unfortunately, many patients who have Cushing's syndrome must undergo surgical exploration of the adrenal glands, especially since definitive therapy (excision) can be accomplished at the same time. When hyperpigmentation is associated with the other features of Cushing's syndrome, an ACTH-producing pituitary tumor should be considered.[16]

*Primary hyperaldosteronism*—Congenital—In the few cases reported, congenital primary aldosteronism has been recognized in the first two decades of life. Diagnostic criteria for congenital aldosteronism are essentially those of Conn's syndrome.

Conn's syndrome—It is important that Conn's syndrome due to adrenocortical adenoma or, rarely, carcinoma is distinguished from nonedematous forms of secondary hyperaldosteronism. It is unfortunate that measurements of aldosterone production will not reliably separate primary from secondary aldosteronism. After

*(Continued on page A-28)*

# MID-MORNING HUNGER-FATIGUE

## *calls for a* HEARTY BREAKFAST

## TEEN-AGERS *need high quality proteins*

# MEAT *is a high quality protein*

. . . studies have supported the view that the calorie intake and ratio of carbohydrate to protein in the breakfast meal influence the post-prandial blood glucose curve, with the higher protein intakes being associated with lower peaks and slower return to fasting levels. (1, 2, 3)

While the source of calories is not critical—an intake of 15 or more gm. of protein slows the blood sugar fall and may be associated with a sense of well-being lacking in low protein breakfasts. (4)


1. Tuttle, Wilson, and Daum: J. Appl. Physiol., **1**, 545, 1949
2. Orent-Keiles, and Hallman: Circ. No. 827, 1949, U.S. Dept. Agric., Washington, D.C.
3. Coleman, Tuttle, and Daum: J. Am. Dietetic Assoc., **29**, 239, 1953.
4. Maurice E. Shils—Mod. Nut. in Health & Disease, Ch. 37, 1960


***AMERICAN MEAT INSTITUTE***

MAIN OFFICE, CHICAGO • MEMBERS THROUGHOUT THE NATION

potassium deficiency has been corrected, urinary tetrahydroaldosterone excretion is usually elevated in Conn's syndrome. Nonedematous hypertensive patients often but not always excrete increased amounts of tetrahydroaldosterone in urine. Indirect assessment of the biologic effects of primary aldosterone excess often must be utilized in establishing the diagnosis. The differentiation of primary from secondary nonedematous hyperaldosteronism is exceedingly difficult, so the essential distinguishing clinical and chemical features of Conn's syndrome will be reviewed here.

Clinical manifestations of headache, polydipsia with nocturnal polyuria, episodic muscular weakness (periodic paralysis), muscular cramping (tetanic), hypertension, and postural hypotension (when present) are strongly suggestive of Conn's syndrome. Laboratory findings of hypernatremia, a hypokalemic alkalosis, hyposthenuria unresponsive to antidiuretic hormone, and a neutral or alkaline urinary pH are confirmatory. The classic features of Conn's syndrome[17] are found in approximately one-fourth of the patients who prove subsequently to have excess secretion of aldosterone.

*Differential diagnosis of primary and secondary hyperaldosteronism*—The diagnostic criteria for the not-so-rare disorder of hyperaldosteronism (perhaps 200 cases have been recognized since 1955) are inadequate. When renal insufficiency supervenes, due to the hypertension, biochemical findings are more difficult to interpret.

Diagnostic signs which help to distinguish primary from secondary (nonedematous) hyperaldosteronism are as follows:

1. Dietary sodium restriction for not less than two weeks results in restoration of positive potassium balance in patients with Conn's syndrome.

2. Persistent hypernatremia (three determinations) usually excludes secondary hyperaldosteronism, as hyponatremia is most often associated with secondary hyperaldosteronism. In Conn's syndrome, hyponatremia may be observed if renal insufficiency is present.

3. Spironolactone will correct abnormal electrolyte metabolism and reverse the clinical manifestations of Conn's syndrome if a high dosage is administered for a prolonged period, e.g., 800 to 1000 mg. ALDACTONE® per day for a minimum of eight weeks. The aldosterone antagonists do not alter the blood pressure in hypertension associated with secondary (nonedematous) hyperaldosteronism. A significant rise in serum potassium is measurable within three days in primary aldosteronism.[18]

4. Inability to conserve potassium on a low potassium intake is a feature of Conn's syndrome but also may be seen in primary renal disease.

5. Preliminary repletion of potassium stores is essential in order to obtain valid studies of urinary aldosterone and tetrahydroaldosterone excretion.

6. Increased plasma volume has been demonstrated in patients with Conn's syndrome. The expanded extracellular fluid volume is not influenced by administration of exogenous mineralo-corticoid or saline infusions in patients with Conn's syndrome, according to Biglieri and Forsham.[19] Plasma volume is not expanded in nonedematous secondary aldosteronism.

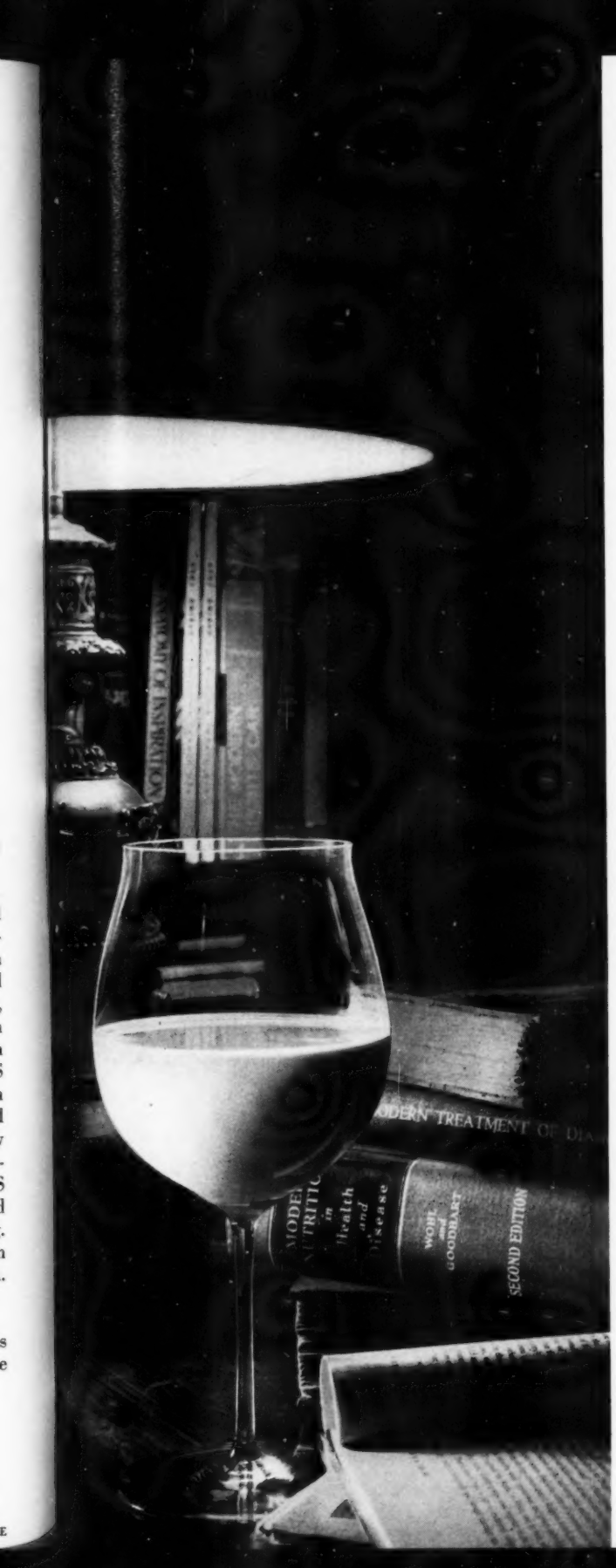
*Virilism due to hypersecretion of adrenal androgen*—Onset of virilism in the adult woman is indicative of an adrenocortical tumor when urinary 17-KS excretion is elevated. When 17-KS excretion exceeds 50 mg. in 24 hours, the presence of large amounts of dehydroepiandrosterone (DHEA) may be detected by a simple procedure, the Allen test.[20] When positive results are obtained, the presence of adrenocortical carcinoma is highly likely.

Hyperplasia of the adrenal cortex which produces virilism may manifest itself in the adult by simple postpuberal hirsutism with little true virilism. Urinary 17-KS excretion usually is only moderately elevated (18 to 30 mg. per 24 hours). Urinary pregnanetriol excretion may be elevated and 17-OHCS excretion may be low. The presence of increased amounts of pregnanetriol in urine suggests a genetic disturbance in steroid hydroxylation (adrenogenital syndrome) which, if highly penetrant, manifests itself prenatally in producing female pseudohermaphroditism which is easily recognizable. A comparison of 17-OHCS and 17-KGS urinary excretions provides a rough screening procedure for elevated pregnanetriol excretion. The 17-OHCS excretion may be low or normal, while the 17-KGS excretion is elevated. (Pregnanetriol is included in the 17-KGS procedure.) Suppression of urinary 17-KS and 17-KGS output by administration of 0.5 mg. dexamethasone every six hours helps to confirm the diagnosis of virilism-producing hyperplasia.

### *Conclusions*

1. Primary adrenocortical insufficiency is proved if ACTH infusion fails to increase the

*(Continued on page A-30)*




*the nutritional approach to weight control*

# Metrecal™

BRAND

DIETARY FOR WEIGHT CONTROL

*...clinical evidence continues to provide reassuring answers to pertinent questions*

Metrecal has been used in a wide variety of medical disorders, including advanced stages of coronary and hypertensive heart disease, peptic ulcer, cirrhosis of the liver, diabetes mellitus and patients with extensive rheumatoid arthritis on steroid therapy. "No serious complications were observed."[1]

Metrecal contains no drugs. It "frees the physician and the patient from the undesirable crutch of the anorexigenic drugs, the metabolic stimulants, and the hydrophilic colloids."[1]

***is Metrecal effective?***

In long-term Metrecal studies of 101 patients, "...the average weight loss was 6.2 pounds in the first week, 4.5 pounds in the second week, 3.7 pounds in the third week and then 2.1 to 3.5 pounds per week from the fourth through the sixteenth week."[3]

In a 12-day study of Metrecal used as the sole source of calories, "the average weight loss for the 100 subjects was 6.5 pounds, or 3.9 per cent of the initial body weight."[2]

*Available in powder and liquid forms in a variety of flavors*

**references:** (1) Roberts, H. J.: Effective Long-Term Weight Reduction—Experiences with Metrecal, Am. J. Clin. Nutrition *8*:817-832 (Nov.-Dec.) 1960. (2) Antos, R. J.: The Use of a New Dietary Product (Metrecal) for Weight Reduction, Southwestern Med. *40*:695-697 (Nov.) 1959. (3) Tullis, I. F.; Allen, C. E., and Overman, R. R.: Simple Effective Weight Reduction: A Clinical Study, Scientific Exhibit, 6th Internat. Cong. Int. Med., Basel, Switzerland, Aug. 24-27, 1960.

41261

Edward Dalton Co.
A DIVISION OF
MEAD JOHNSON & COMPANY
EVANSVILLE 12, INDIANA

*Quality products from nutritional research*

level of blood cortisol or excretion of urinary cortisol metabolites (17-OHCS and 17-KGS).

2. Secondary adrenocortical insufficiency is demonstrated by the failure of injected bacterial pyrogen to increase blood cortisol levels in an individual responding normally to ACTH. Failure of urinary 17-OHCS to increase after 750 mg. of Su 4885 every four hours is also indicative of adrenocorticotropin deficiency.

3. Cushing's syndrome of cortisol excess is confirmed by (1) elevated urinary 17-OHCS excretion which may not be suppressed by oral administration of 0.5 mg. of the potent cortisol analogue dexamethasone every six hours, (2) absence of diurnal variation of cortisol concentration in plasma, and (3) elevation of urinary free cortisol excretion.

4. In Cushing's syndrome, suppression tests using dexamethasone or fluoroprednisolone indicate the presence of an autonomously functioning tumor when a dosage of 8 mg. per day fails to suppress 17-OHCS output.

5. Conn's syndrome of mineralo-corticoid excess may be differentiated from secondary (nonedematous) hyperaldosteronism by (1) restoration of positive potassium balance by sodium restriction; (2) persistent hypernatremia; (3) the demonstration (in a patient with hypokalemic alkalosis and hypertension) of a rise in serum potassium (usually greater than 1.0 mEq. per liter per day) during administration of spironolactone (Aldactone) in dosages exceeding 1000 mg. per day for three days (perhaps the simplest and most reliable screening procedure available); and (4) demonstration of an increased plasma volume (more than 20 per cent over normal).

6. Virilism due to excessive adrenocortical androgen production is associated with elevated urinary 17-KS excretion. Elevations in excess of 50 mg. per day and detection of DHEA by the Allen test are strong evidence for the presence of an adrenocortical carcinoma. Low or normal amounts of 17-OHCS in the presence of raised levels of 17-KGS most probably are due to elevated excretion of pregnanetriol and are presumptive evidence of an inborn error of cortisol biosynthesis, the adrenogenital syndrome.

## REFERENCES


1. Waterhouse, R.: Case of suprarenal apoplexy. Lancet 1:577, 1911.
2. Friderichsen, C.: Nebennierreapoplexie bei kleinen Kindern. Jahrb. Kinderh. 87:109, 1918.
3. Melby, J. C. and Spink, W. W.: Comparative studies on adrenocortical function and cortisol metabolism in healthy adults and in patients with shock due to infection. J. Clin. Invest. 37:1791, 1958.
4. Jenkins, D., Forsham, P. H., Laidlaw, J. C., Reddy, W. J. and Thorn, G. W.: Use of ACTH in diagnosis of adrenal cortical insufficiency. Am. J. Med. 18:3-14, 1955.
5. Christy, N. P., Wallace, E. Z. and Jailer, J. W.: The effect of intravenously administered ACTH on plasma 17, 21-dihydroxy-20-ketosteroids in normal individuals and in patients with disorders of the adrenal cortex. J. Clin. Invest. 34:899, 1955.
6. Silber, R. H. and Porter, C. C.: The determination of 17, 21-dihydroxy-20-ketosteroids in urine and plasma. J. Biol. Chem. 210:923, 1954.
7. Wu, C. and Mason, H. L.: The chemical determination of cortisol in blood plasma. Proc. Staff Meet. Mayo Clin. 33:627, 1958.
8. Melby, J. C., Egdahl, R. H. and Spink, W. W.: Secretion and metabolism of cortisol after injection of endotoxin. J. Lab. & Clin. Med. 56:50, 1960.
9. Melby, J. C.: Assessment of adrenocorticotropic activity with bacterial pyrogen in hypopituitary states. J. Clin. Invest. 38:1025, 1959.
10. ——: Assessment of adrenocorticotropic activity in man following steroid therapy. First International Congress on Endocrinology, Copenhagen, Denmark, July 1960.
11. Liddle, G. W., Estep, H. L., Kendall, J. W., Williams, W. C. and Townes, A. S.: Clinical application of a new test of pituitary reserve. J. Clin. Endocrinol. 19:875, 1959.
12. Birke, G. and Diczfalusy, E.: Fluctuation in the excretion of adrenocortical steroids in a case of Cushing's syndrome. J. Clin. Endocrinol. 16:286, 1956.
13. Doe, R. P., Vennes, J. A. and Flink, E. B.: Diurnal variation of 17-hydroxycorticosteroids, sodium, potassium, magnesium and creatinine in normal subjects and in cases of treated adrenal insufficiency and Cushing's syndrome. J. Clin. Endocrinol. 20: 253, 1960.
14. Ross, E. J.: Urinary excretion of cortisol in Cushing's syndrome: Effect of corticotropin. *Ibid.*,[13] p. 1360.
15. Liddle, G. W.: Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome. *Ibid.*,[13] p. 1539.
16. Salassa, R. M., Kearns, T. P., Kernohan, J. W., Sprague, R. G. and MacCarty, C. S.: Pituitary tumors in patients with Cushing's syndrome. J. Clin. Endocrinol. 19:1523, 1959.
17. Conn, J. W.: Primary aldosteronism, a new clinical syndrome. J. Lab. & Clin. Med. 45:3, 1955.
18. Higgins, H. P. and O'Sullivan, M.: Use of an aldosterone antagonist in diagnosis of primary hyperaldosteronism. Canad. M.A.J. 83:1289, 1960.
19. Biglieri, E. G. and Forsham, P. H.: Studies on the expanded extracellular fluid and the responses to various stimuli in primary aldosteronism. Am. J. Med. 30:564, 1961.
20. Allen, W. M., Hayward, S. J. and Pinto, A.: A color test for dehydroisoandrosterone and closely related steroids of use in the diagnosis of adrenocortical tumors. J. Clin. Endocrinol. 10:54, 1950.

# What's happening in Medicine ?

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

## ATARAXICS AND DISCHARGE RATES

American Psychiatric Association, Chicago:

• Long-term results with ataractic drugs and milieu therapy in patients at the Veterans Administration Hospital, Northport, N. Y., show that the present discharge rate differs little from that in mental hospitals in the past. While ataractic drugs undeniably have greatly improved the hospital atmosphere by quieting the patients and may have caused individual patients to "feel better," it is clear that additional therapeutic devices are required if the permanent discharge rate from large mental institutions is to be materially increased.—Dr. Henry Tanner, Northport, N. Y.

• Suicide attempts are not rare in childhood and adolescence. In a survey during 1960 at the Bellevue Psychiatric Hospital Unit of Bellevue Hospital Center, New York, 106 of 900 consecutive patients less than 17 years old were admitted for suicide attempts. Twenty-one patients were less than 12 years old. Behavior and character disorders, depressive reactions and adjustment reactions were diagnosed in the majority of patients. Outstanding dynamic factors were (1) anger at another person, internalized in the form of guilt and depression; (2) a desire to call attention to the patient's problems; and (3) reaction to feelings of inner disintegration or response to a hallucinatory command.—Dr. James M. Toolan, New York.

## PREVENTING ADAMS-STOKES SEIZURES

American College of Physicians, Miami Beach:

• Patients with malfunctioning conductive tissue have no safety margin; thus a temporary slight worsening of conduction will produce a period of asystole with loss of consciousness. Chlorothiazide changes the ratio of extracellular to intracellular potassium in the conductive tissue only about 15 to 20 per cent, but this is enough to improve conduction, increase the safety margin, and prevent seizures. Seven patients with a long history of Adams-Stokes seizures were given sufficient chlorothiazide to lower the plasma potassium 0.6 to 1.1 mEq. per liter. The lessened incidence of seizures was not accompanied by any change in plasma pH even though the plasma bicarbonate rose slightly in some cases.—Dr. Louis Tobian, University of Minnesota Medical School, Minneapolis.

• A six year follow-up of the Framingham study showed that elevation of serum cholesterol levels (245 mg. per cent or more) was associated with more than a threefold increase in cardiovascular risk in men aged 40 to 59 but contributed only slightly to increased risk among women.—Dr. W. B. Kannel, Framingham, Mass.

### Hormones in Aging

American Geriatrics Society, New York:

• The postmenopausal state is a unique example of hormonal deficiency resulting from the aging process. In the past, endocrinologists have dismissed the sharp decline in estrogen production during menopause as being of little consequence to the body as a whole. Whereas emphasis once was placed on the psychologic adjustment to the transitional phase, the question now being raised is whether continuing estrogen therapy after the menopause might be routinely indicated. Such treatment might help inhibit osteoporosis and atherosclerosis. Similarly, the administration of male hormones to elderly men for short periods may increase nitrogen retention and possibly improve muscle function, but it would seem to have little over-all rejuvenating effect.—Dr. Reginald A. Shipley, Western Reserve University School of Medicine, Cleveland.

• In later life, the will to live and adapt to stressful life situations is often undermined by a little-recognized phenomenon which may be called "the preparation for death." This phenomenon is characterized by a gradual withdrawal of the organism from participation in the ongoing life processes. There is a withdrawal of emotional investment in meaningful objects, both animate and inanimate, and a loss of interest in and disengagement from life, as if the organism were preparing for final isolation and death. To counter these phenomena, there are life-giving, health-sustaining motivations which must be practiced and continually enhanced throughout life. These are (1) maintenance of the best possible physical health; (2) a wide variety of gratification sources, including regular work, creative channels and social responsibilities; (3) recognition of self-limitations and potentialities; and (4) adaptability to stressful situations.—Dr. Jack Weinberg, University of Illinois College of Medicine, Chicago.

### Postpartum Psychoses

International College of Surgeons, North American Federation, Chicago:

• The physician attending a pregnant woman is in a strategic position to function as the ideal mental hygienist of childbirth. Without being a psychiatrist, he can greatly contribute to the emotional well-being of the mother through encouragement and reassurance. All pregnant women should be allowed to express their fears, anxieties and sources of apprehension. Group discussions in antenatal clinics may be an effective method. The greatest immediate danger in all postpartum psychoses is suicide or infanticide, or both. Hospitalization is imperative and psychotherapeutic drugs, either ataraxics or antidepressants, may be necessary. Electroshock therapy may be used with impunity, both during pregnancy and after delivery.—Drs. Alfred Wiener and Richard M. Steinhilber, Mayo Clinic and Mayo Foundation, Rochester, Minn.

• Excessive tissue trauma frequently causes contracture of the bladder after prostatectomy. Paradoxical though it may seem, the more proficient the resection, the higher is the incidence of contracture and diaphragm formation at the bladder neck. Every care must be taken to work distally, no matter how dangerous surgery in the area of the verumontanum is thought to be.—Dr. John C. Campbell, Mayo Clinic, Rochester, Minn.

### Cerebral Tumors Scanned

American Radium Society, Colorado Springs:

• In 344 patients, brain tumors were localized with 85 per cent accuracy by scintillation scanning. The test was 94 per cent accurate in screening normal subjects. In only two patients were results falsely reported as positive.—Dr. Edward B. Schlesinger, Columbia-Presbyterian Medical Center, New York.

**Upjohn**

*75th year*

Man does not live by bread alone.
If he did, medicine would be purely a science, concerned only with "bread to nourish the body."

Thoughtful physicians have long recognized the equal essentiality of "hyacinths to feed the soul." This is the *art* of medicine.

If yours is a typical practice, many of the patients who come to you have no demonstrable somatic pathology. Yet their symptoms often are myriad: low back pain, recurrent headaches, insomnia, anorexia, chronic fatigue, apathy, inability to concentrate, "blues."

Most of these patients are not candidates for psychiatry, and certainly not for tranquilizers or sedatives. They are candidates for the simple psychomotor effect of Monase. Tests in more than 2,000 such patients justify the expectation that Monase will enable many of these patients to sleep better, eat better, and feel better.

**For the 4 out of 10 patients with no demonstrable pathology,† consider**

# Monase*

*TRADEMARK, REG. U.S. PAT. OFF.
†ESTIMATED AVERAGE IN GENERAL PRACTICE
COPYRIGHT, 1961, THE UPJOHN COMPANY

**Description:** Monase is etryptamine acetate, a unique non-hydrazine compound, developed in the Upjohn Research Laboratories.

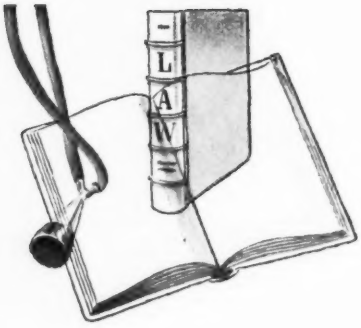
**Indications:** Various depression states: manic-depressive reaction, depressed type; involutional psychotic reactions with depressed features; psychotic depressed reactions; psychoneurotic depressive reactions; psychiatric disorders with prominent depressive symptoms or features; transient situational personality disorders with pathological depressive features.

**Dosage:** 30 mg. daily in divided doses. Initial benefit may be observed within 2-3 days, but maximum results may not be apparent until after 2 or more weeks. Adjustment of dose to individual response should be effected in increments or decrements of 15 mg. daily at weekly intervals. The daily maintenance dose ranges between 15 and 45 mg. In schizophrenics, 30 mg. daily may be useful as an adjunct in activating these patients or brightening their mood.

**Contraindications and Precautions:** There are no known absolute contraindications to Monase therapy. However, the drug should be used with caution in schizoid or schizophrenic patients, paranoids, and in patients with intense anxiety, as it may contribute to the activation of a latent or incipient psychotic process. Patients with suicidal tendencies should be kept under careful observation during Monase therapy until such time as the self-destructive tendencies are brought under control.
Patients who are on concomitant antihypertensive therapy should be watched carefully for possible potentiation of hypotensive effects. Added caution should be employed in patients with cardiovascular disease in view of the occasional occurrence of postural hypotension, and the possibility of increased activity as a result of a feeling of increased well being.
Despite the fact that liver damage or blood dyscrasias have not been reported in patients receiving Monase, as is the case with any new drug, patients should be carefully observed for the development of these complications. Monase should probably not be used in patients with a history of liver disease or abnormal liver function tests. Also the usual precautions should be employed in patients with impaired renal function, since it is possible that cumulative effects may occur in such patients.
Monase should be employed with caution in patients with epilepsy since the possibility exists that the epileptic state may be aggravated. Also because of its autonomic effects, therapy with Monase may aggravate glaucoma or may produce urinary retention. Monase must not be administered concomitantly with imipramine. In patients receiving Monase caution should be employed in administering the following agents or related compounds in view of possible lowering of the margin of safety: meperidine, local anesthetics (procaine, cocaine, etc.), phenylephrine, amphetamine, alcohol, ether, barbiturates or histamine.

**Toxicity and Side Effects:** The side effects observed in patients on Monase therapy in general have been mild and easily managed by symptomatic therapy or dose reduction. If such side effects persist of are severe, the drug should be discontinued. Alterations in blood pressure, usually in the form of postural hypotension, or more rarely, an elevation of blood pressure have been reported. Other side effects include allergic skin reactions and drug fever and those that appear to be dose related since they are more likely to occur when the daily dose exceeds 60 mg. These are nausea and gastrointestinal upset, headache, vertigo, palpitation, dryness of the mouth, blurred vision, over-stimulation of the central nervous system, restlessness, insomnia, paradoxical somnolence and fatigue, muscle weakness, edema, and sweating. Following sudden withdrawal of medication in patients receiving high doses for a prolonged period. There may occur a "rebound" withdrawal effect which is characterized by headache, central nervous system hyperstimulation and occasionally hallucinations.

**Supplied:** Monase, compressed tablets, 15 mg. in bottles of 100.




# Forensic Medicine

OLIVER C. SCHROEDER, JR.*

## Blunt Violence

FRANCIS J. HATCH†

*St. Vincent's Hospital, Santa Fe, New Mexico*

**Editorial Comment**

Cause of injury or death is a major medicolegal problem. Liability in law is based on such a causal relation. A traumatic blow to a person, if undiscovered by medicine, will be ignored by the law. Civil and criminal litigation will then suffer from the lack of accurate, truthful facts. Dr. Hatch has illuminated the medicolegal dangers inherent in blunt violence to the human body.—Oliver C. Schroeder, Jr.

An elderly shopkeeper, counting the day's receipts, is struck down from behind by a hammer in the hands of an assailant intent on robbery. The soft tissues of the shopkeeper's scalp muffle the sound of breaking bone fragments being driven into brain by the vigorous hammer blows. Next door a carpenter is driving nails into planks with equally vigorous blows, and a house is being built.

While a wide moral and legal chasm separates the robber and the carpenter, their acts are fundamentally similar—only the results differ. Each man has received energy (the ability to do work) from the food he has eaten. As he raises his arm he transfers part of that energy to the hammer in his hand. The higher he raises the hammer, the more energy is transferred. At the apex of its swing the hammer pauses. Because of its position it can now do work itself. If it were allowed to fall, it might produce a bump on a person's head or drive a small tack into wood. However, each man knows that if he directs the hammer and accelerates it (transfers additional energy), he can make it work more efficiently and the job will be done sooner. At the end of its downward course, the hammer is stopped almost instantly by the resistance (inertia) of

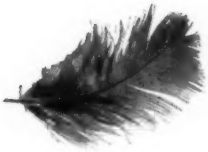
FRANCIS J. HATCH

*(Continued on page A-44)*

*Director, Law-Medicine Center, and Professor of Law, Western Reserve University, Cleveland, Ohio.

†Pathologist, St. Vincent's Hospital, Santa Fe, New Mexico.

# It takes so little to trigger an asthmatic attack...



## it takes so little MORE to control it... the simple addition of ATARAX to your classic anti-asthmatic therapy increases therapeutic success even in difficult patients

**Each MARAX tablet contains: ATARAX®** (hydroxyzine HCl) 10 mg.—an antihistaminic tranquilizer beneficial in bronchial asthma and allergy.[1] **Ephedrine sulfate** 25 mg.—to reduce congestion. **Theophylline** 130 mg.—for bronchospasmolysis.

"Superiority of [MARAX] seems attributable to the inclusion in it of hydroxyzine in place of the conventional barbiturates."[2] In a series of patients generally refractory to the usual antiasthmatics, and who required steroids in order to obtain temporary relief, 70% showed good to excellent symptomatic relief with MARAX. Patients "...slept more comfortably and breathed more easily. The characteristic asthma wheeze was either markedly reduced or entirely relieved."[3]

If your asthma patients do not respond to standard therapy, they may need the "little MORE" that MARAX offers.

# MARAX®

Usual adult dosage: One tablet 2 to 4 times daily. Full prescription information on request. Supplied: Bottles of 100 light blue, scored tablets. Prescription only.

**References:** 1. Santos, I. M. H., and Unger, L.: Ann. Allergy 18:172 (Feb.) 1960. 2. Charlton, J. D.: Ann. Allergy, In press. 3. Shaftel, H. E.: Clin. Med. 7:1841 (Sept.) 1960.

ROERIG Rx

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being®

the target and, in a fraction of a second, the accumulated energy is transferred to the stationary object through an area of less than one square inch. That portion of the skull underneath the hammer is set into motion in the same direction. This change from rest to motion takes place so rapidly that the rest of the skull tends to remain behind. Therefore a fragment of bone is broken off and driven into the victim's brain. In the same manner the building remains stationary while the nail is driven forward into the wood.

The principles embodied in these illustrations were stated many years ago by Sir Isaac Newton when he said, "Every body continues in a state of rest or uniform motion in a straight line except insofar as it may be compelled to change that state by the action of some outside force," and, "Change of motion is proportional to force applied."

Here is equality with a vengeance. All living organisms and inanimate objects are subject to these laws, and neither one's position on the evolutionary scale nor on the stock exchange will modify their enforcement.

Injury by blunt violence is produced by relatively broad, flat surfaces, the damage being caused by jarring, crushing or tearing. Representative agents would include fists, feet, clubs, hammers, saps and automobiles, as well as the pavement, curbing, or bar rail on which the victim may land.

In the urban, metropolitan area of greater Cleveland, one in every 50 deaths is the result of blunt violence. In this category would be included all traffic accidents, injury by flying objects, falls, suicidal jumps and dives, and homicidal assaults with blunt weapons.

Injury by blunt violence produces characteristic marks on the surface of the body. These may be contusions, abrasions or lacerations, or combinations of these within the single area of injury. Contusions (bruises) are caused by blows which rupture the small blood vessels within the skin. Bleeding into the tissues occurs, resulting in a bluish-black patch of discoloration. With the passage of time, the broken vessels heal and the extravasated blood is removed; the patch of discoloration becomes paler and is replaced by a yellowish-brown and reddish-brown mottling. While this color change is no more pleasing to the eye, it does indicate that several days have elapsed since the injury.

Abrasions are produced by a forcefully applied object moving across the skin and scraping away some of the superficial skin layers. Scratches are linear abrasions. Lacerations are splits or tears in tissue. A laceration may be differentiated from a cut by its abraded or bruised margins. A heavy blow which stretches the skin excessively or a blow to skin stretched over a bony prominence may result in tearing. Blunt violence may leave little or no evidence of external injury while causing severe, often fatal damage to vital organs (figure 1). Clothing may protect the skin while the organs are being crushed. Almost any hoodlum knows that a man can be beaten to death with a sock containing a bar of laundry soap without leaving a mark on the victim's body. How many persons have been treated for lacerations of face and scalp while they bled to death from a torn spleen or liver reposing beneath the surface of an unmarked belly? Here lies a real danger to the medical practitioner seeking to treat his injured patient.

### *Injuries to Head and Spinal Cord*

In reviewing any series of autopsies done on persons who have died as the result of blunt injury, it becomes evident that the head is a particularly vulnerable target. The brain is a mass of soft tissue of approximately the consistency of a ripe banana. The skull, which encases it, is composed of brittle bony plates which form sharp splinters when broken. The floor of this case, on which the brain rests, has several sharp bony ridges and spines. In addition, the brain is enclosed by a tough membrane, the edges of which are closely approximated to vital areas. Large, thin-walled blood vessels course over the surface of and through the brain. The only opening of any significant size is in the back portion of the base. This is the foramen magnum (big hole) which is less than 1¼ in. in maximum diameter. The spinal cord passes through this orifice into the spinal canal. These structural features are im-

*(Continued on page A-46)*

***to combat the three-pronged assault of urinary tract infections — bacteriuria — tissue infection — discomfort***

# UROBIOTIC®

COSA-TERRAMYCIN® — SULFONAMIDE — ANALGESIC

*Only* **UROBIOTIC** *contains:* **OXYTETRACYCLINE** (with glucosamine for enhanced absorption) — notable for its wide tissue distribution, high urinary concentration, excellent toleration and proven antibiotic effectiveness against even so troublesome an invader as *Pseudomonas;* **SULFAMETHIZOLE** — an unusually soluble, highly active sulfonamide; **PHENYLAZO-DIAMINO-PYRIDINE** — for effective local analgesia.

*IN BRIEF*

**INGREDIENTS:** Each Urobiotic capsule contains 125 mg. Terramycin® (oxytetracycline) with 125 mg. glucosamine HCl, 250 mg. sulfamethizole, and 50 mg. phenylazo-diamino-pyridine HCl.

**INDICATIONS:** Urobiotic is indicated in the treatment of a number of common genitourinary infections caused by susceptible organisms. It may also be used prophylactically before and after genitourinary or pelvic surgery, following instrumentation procedures, during the use of retention catheters, and in patients with conditions such as cord bladder or cystocele.

**DOSAGE:** In adults, a dose of 1 or 2 capsules four times daily is suggested, depending upon the severity and response of the infection. In children 60 to 100 lbs., the suggested average dose is 1 capsule four times daily; in children under 60 lbs., 1 capsule three times daily. Therapy should be continued for a minimum of 7 days or until bacteriologic cure is effected in acute urinary tract infections.

**CONTRAINDICATIONS:** Urobiotic may be contraindicated in patients with chronic glomerulonephritis, hepatitis, hepatic failure, uremia, and obstructive lesions of the urinary tract, and should not be used in patients sensitive to any of its components.

**PRECAUTIONS:** The use of broad-spectrum antibiotics may, in rare cases, result in an overgrowth of nonsusceptible organisms, such as monilia or staphylococci. Should such superinfection occur, therapy with Urobiotic should be discontinued and specific therapy instituted as shown by susceptibility testing. The use of sulfonamides may cause renal crystalluria or skin rash, as well as other toxic or sensitivity reactions. If any of these occur, discontinue use.

**SUPPLIED:** Urobiotic capsules, yellow-and-grey, bottles of 50.

Pfizer

*More detailed professional information available on request.*

*PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York Science for the world's well-being®*

FIGURE 1. This infant was found dead and was brought to the coroner's office with a history of several falls.

a. Note that only a small bruise is visible on the left side of the forehead. However, deflection of the scalp (b) revealed a massive hemorrhage into the underlying tissues and several fractures of the skull. Subsequent examination also disclosed extensive brain damage—a vivid demonstration that there need be little or no evidence of injury on the surface of the body associated with fatal damage to underlying structures.

portant when considering a head injury.

Lacerations of the scalp result in spectacular bleeding. However, as long as the bleeding is controlled, its chief importance is as an indication that more serious damage may have been done to underlying structures. Fatal head injuries often occur with no external marks. In fact, the victim does not even have to be hit on the head. Skull fractures and brain damage can result from the force transmitted to the base of the skull by a blow on the jaw or a fall in which the victim lands on his buttocks or heels.

Persons with fractured skulls sometimes bleed from their ears, but often do not. If the victim has been struck hard enough to fracture his skull, it is probable that damage has also been done to the brain and its blood vessels. Bleeding inside the skull is extremely serious. An expanding pool of blood within the cranial vault cannot escape—and neither can the brain. As the pressure increases the brain is compressed toward the foramen magnum. The medulla oblongata of the brain is pushed into this opening, which is too small to receive it. Since the areas controlling heartbeat and respiration are in the medulla, the victim will soon die if he does not receive prompt medical attention. Often this intracranial bleeding is slow, and neither the victim nor those who examine him may suspect that he has been seriously injured. Hours later, after the incident has been forgotten, the slowly accumulating pool of blood will begin to exert sufficient pressure, and the victim will become drowsy, unconscious and finally will die. If the original incident was not witnessed and there are no external injuries, the injured person may be written off as having died during his sleep as the result of a heart attack.

The brain may be damaged by impacts which do not cause fracture of the skull or bleeding. Blows to the head are transmitted as shock waves through the bone, through the fluid which cushions the brain, and through the brain tissue. The brain will be bruised on the side receiving the injury, and frequently there will be even more bruising on the opposite side. While the mechanism of this *contrecoup* type of injury is not certain, it is possible that the skull and its contents behave in a

fashion similar to a lens, focusing the waves from the original shock and its reverberations to produce a second point of maximum disturbance on the opposite side of the brain. Lesser shocks may render a person temporarily confused or unconscious without causing any visible damage to the brain. But some permanent injury is probably done, since the result of multiple blows of this type is the all-too-familiar tragic figure who comes bobbing and weaving out of his corner when the doorbell rings.

Blows to the head may move the brain and its covering with respect to each other, causing the sharp margins of the protecting membranes to slice into or bruise the adjacent brain tissue. A heavy impact may move the skull off its attachment to the spine, tearing apart the spinal cord and brain. Crushing injuries may result in the type of horror referred to as the "toothpaste phenomenon" in which the brain is squirted from its case.

The brain and spinal cord are two parts of a single unit. The spinal cord lies within a bony canal formed by the vertebral column or spine. The spine consists of a flexible column of 33 stacked vertebrae bonded together by cartilage and muscle. A violent impact may break the spine or move one or more of these vertebrae with respect to the others. Depending on the amount of movement, the spinal cord may be compressed, bruised, lacerated or torn apart. Rough handling of the victim by inexperienced persons may cause permanent damage in cases where the injury was originally slight.

The important features of any injury to the spine are the site and amount of damage to the spinal cord. A broken back or dislocated vertebra can be repaired and will heal rapidly, but a torn spinal cord will result in a permanent defect. If the site of injury is high in the neck there is complete paralysis of all limbs; if the victim survives, he will spend the rest of his life in a respirator. He will have no control over urination or bowel movement and his sexual functions will be destroyed. If the damage is at a lower level there are fewer deficiencies. Often, an individual who appears to be hopelessly paralyzed will regain all or part of his functions as the swelling in the area of injury decreases. In such cases, the nerve fibers have been compressed but not permanently damaged, and there is return to normal function when the pressure is relieved.

### *Injuries to the Neck and Chest*

Blunt violence to the neck may crush the larynx or trachea or may cause hemorrhages and swelling of the soft tissues in the throat. Following the injury there may be rapid or gradual obstruction of the airway and strangulation. A sharp blow to the side of the neck, beneath the jaw, may cause unconsciousness or death, since violent stimulation of nerve endings in this area will slow or even stop the heart.

The chest is a bony cage consisting of 24 ribs. Twenty-two of these are attached to the spine in back and to the breastbone (sternum) in front. The last two (floating ribs) are attached only to the spine, the front ends lying free. Within the chest cavity the heart and each lung are isolated, each being completely encased in a fibrous sac. The central partition (mediastinum) separates the right and left sides. The trachea, esophagus and large blood vessels to and from the heart are within this partition.

Blunt impacts to the chest may crush the heart between the breastbone and spine (figure 2). A lesser impact may cause a tear in the surface of the heart. As the enclosing pericardial sac becomes filled with blood there is increased pressure on the heart (cardiac tamponade) until it can no longer beat, and the victim dies. Impacts may also produce sudden traction with tearing of the large blood vessels within the mediastinum. In such cases a person will hemorrhage into his chest cavity and die within a few minutes. Sudden compression of the lungs may cause them to burst. All of these things can occur without any evidence of injury on the surface of the body and without any fractures. If ribs are broken, the jagged ends may tear into the heart or lungs. If the chest wall is perforated, providing free communication with the outside, the lung on that side will collapse. In such cases the vic-

*(Continued on page A-49)*

**Lederle**– where innovation and improvement in immunizing agents is a tradition

Lederle immunizing agents reflect the tradition of constant research to discover the new and improve the old. A case in point: Lederle Smallpox Vaccine is now produced from vaccinia virus cultured in chick embryos—a radical change—for the better—from the older calf lymph technique. The result: an AVIANIZED® vaccine with lessened danger of excessive scarring or secondary infection...a superior vaccine for routine use...and far more quickly obtainable in quantity to meet a public health emergency...Other Lederle immunologic agents—

Antirabies Serum
Rabies Vaccine
Botulism Antitoxin
Catarrhalis Vaccines
Cholera Vaccine
Diphtheria-Tetanus Toxoids
Gas Gangrene Antitoxin Polyvalent
Influenza Virus Vaccine Polyvalent
Mumps Vaccine
Pertussis Vaccine
Poliomyelitis Immune Globulin
Rocky Mountain Spotted Fever Vaccine
Staphylococcus Toxoid
Tetanus Antitoxin
Tetanus-Gas Gangrene Antitoxin
Tetanus Toxoids
TRI-IMMUNOL* Diphtheria-Tetanus Toxoids and Pertussis Vaccine
Typhoid-Paratyphoid Vaccine
Typhus Vaccine
POLLIGENS® Pollen Antigens Eastern
POLLIGENS® Pollen Antigens Western
Mixed Grasses
Ragweed Combined
Allergenic Extract Dust (House)

Request complete information on indications, dosage, precautions and contraindications from your Lederle representative or write to Medical Advisory Department.
*Trademark

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

FIGURE 2. Lacerations of the heart and aorta resulting from the impact of a car's steering post against the chest, crushing the heart between the breastbone and spine. The victim was driving a car which struck a concrete abutment.

tim may die quickly, in shock, or may survive long enough to asphyxiate slowly.

### *Injuries to Abdominal Organs*

Unprotected as they are, the abdominal organs are often injured by blunt violence. The liver and spleen are the most frequent sites of injury. Both are soft, structurally weak organs covered by thin fibrous capsules and traversed by large thin-walled blood vessels. Sudden compression, twisting or jarring, often not severe enough to cause damage elsewhere, may cause lacerations of these organs followed by rapidly fatal intraabdominal hemorrhage.

The stomach and intestines are thin-walled and soft, but owing to their extreme mobility, they are not as frequently damaged. However, anyone who has ever dropped a paper bag filled with water on a sidewalk can visualize the effect of a sudden impact on a fluid-filled stomach or urinary bladder. Physicians in Napoleon's army noted the high incidence of bladder rupture associated with blast injuries. Oddly enough this was seen only among veteran soldiers. The problem was resolved with the realization that, characteristic of soldiers in any army, the new recruits went into battle with empty bowels and bladder.

Bursting organs, ruptured blood vessels, and jagged fragments of broken bones tearing through tissues inevitably result in massive bleeding. If a person loses 30 per cent of his blood volume by sudden hemorrhage he will die. Loss of a similar volume by slow bleeding over a week would not cause severe distress, as the body would have time to react and would compensate for the loss by producing greater numbers of blood cells and retaining a proportion of the fluids which are normally excreted.

Frequently the substance of the liver or spleen may be torn while its capsule remains intact. Following the injury bleeding will occur within the organ, gradually increasing its volume, until the stretch limits of the capsule are exceeded. The capsule tears and a rapid fatal hemorrhage may follow. A similar situation may result from a nonperforating laceration of a blood vessel, subsequent perforation being caused by pressure of the blood stream against this weak point in the vessel wall. Such delayed hemorrhages may occur hours or even days after the original injury.

### *Mechanism of Injury*

The human body is a self-regulating mechanism. As in any self-regulating machine, con-

*(Continued on page A-51)*

# not a general-purpose antibiotic

Albamycin is not a broad-spectrum antibiotic, recommended for routine infections. It is specific for staphylococci (including resistant strains), and its use alone should (with the exceptions listed below) be limited to those cases in which staph is known or strongly suspected to be the causative organism.

# Albamycin*

**Indications** — Albamycin is indicated in the treatment of staphylococcic infections, particularly in patients sensitive to other antibiotics or in the infections in which the organism is resistant to other antibiotics and sensitive to Albamycin, and in urinary tract infections due to microorganisms resistant to other commonly employed antibacterial agents but sensitive to Albamycin — notably certain strains of Proteus.

**Administration and Dosage — Capsules and Syrup:** The recommended dosage in adults is 500 mg. every twelve hours or 250 mg. every six hours, continued for at least forty-eight hours after the temperature has returned to normal and all evidence of infection has disappeared. In severe or unusually resistant infections, 0.5 Gm. every six hours or 1 Gm. every twelve hours may be employed. The dose for children is 15 mg. per kilogram of body weight per day for moderately acute infections; this may be increased to 30 to 45 mg. per kilogram of body weight per day for severe infections. These doses may be administered on schedules similar to those for adults.

**Parenteral: Intramuscularly**—5 cc. of Albamycin solution may be used directly by slow injection deep into the gluteal muscle.

**Intravenously** — it is recommended that 5 cc. of Albamycin solution be diluted further with 250 to 1000 cc. of sterile injection solution of sodium chloride, Darrow's solution, or Ringer's solution and administered by intravenous infusion, or by diluting to a suitable quantity and administered by continuous drip infusion. **Do not use with dextrose solution.** When it is necessary to use a smaller volume intravenously, 5 cc. of Albamycin solution may be diluted to a minimum of 30 cc. with one of the above diluents and administered slowly over a period of five to ten minutes to avoid irritation of the vascular endothelium. The dosage for adults is 500 mg. Albamycin administered either intramuscularly or intravenously every twelve hours. For children with moderately acute infections, the dosage is 15 mg. per kilogram of body weight per day. The daily dosage should be administered in two divided doses at intervals of twelve hours. As soon as the patient's condition permits, parenteral Albamycin should be replaced with oral Albamycin therapy.

**Side Effects** — Albamycin is a substance of low toxicity but is capable of inducing urticaria and maculopapular dermatitis. Leukopenia, which was rapidly reversible, has been reported in approximately 1% of cases. All of these side effects disappear rapidly upon discontinuance of the drug. In a certain few patients, a yellow pigment has been found in the plasma. This pigment is a metabolic by-product of the drug which, however, may interfere with determination of bilirubin and icteric index. Its presence is not associated with abnormal liver function tests or liver enlargement.

**Available** — Albamycin, 500 mg., sterile, Mix-O-Vial.† Each Mix-O-Vial contains: 500 mg. Novobiocin (as novobiocin sodium), also 175 mg. Nicotinamide; 0.47 cc. N,N-Dimethylacetamide; 42.3 mg. Benzyl alcohol; 4.23 cc. water for injection. Albamycin Capsules. Each capsule contains: 250 mg. Novobiocin (as novobiocin sodium). Albamycin Syrup. 125 mg. per 5 cc. Each 5 cc. (one teaspoonful) contains: 125 mg. Novobiocin (as novobiocin calcium). Preserved with methylparaben, 0.075%, and propylparaben, 0.025%.

*Trademark, Reg. U. S. Pat. Off. — The Upjohn brand of crystalline novobiocin sodium. †Trademark, Reg. U. S. Pat. Off.

The Upjohn Company
Kalamazoo, Michigan

Upjohn

trol is exercised by feedback; that is, part of the output is returned to and regulates the input. In the arterial walls there are nerve endings which are sensitive to pressure. If the blood pressure rises, this information is conveyed to the brain and modifies the activity of the control center, resulting in outgoing nerve impulses that slow the heart and dilate the blood vessels. If the blood pressure drops, signals from the feedback system cause an increase in the heart rate and constriction of the blood vessels.

Abnormalities in blood pressure are caused by defects in the heart and blood vessels or by strong signals from other parts of the nervous system which override the control center. Thus the nervous impulses resulting from an ice-water enema, a kick in the testicles, or bad news from home may cause a sudden drop in blood pressure and fainting. This is primary shock. If sudden massive hemorrhage occurs, the feedback system will transmit the fall in blood pressure, and the nervous system, heart and blood vessels will respond. If too much blood has been lost, the blood pressure will remain low, and the victim will remain unconscious or will die. Therefore, primary shock is the rapid onset of an inadequate circulation caused by sudden loss of a large amount of blood, by a defect in the circulatory system (e.g., heart attack), or by the loss of the usual neural control of the heart and blood vessels. If these conditions are not corrected, all of the tissues of the body are affected. They receive an inadequate supply of food and oxygen, and they are poisoned by the accumulation of their own waste products. The tissues forming the walls of the small blood vessels are affected and are no longer able to contract. Fluid from the blood leaks through the vessel walls into the surrounding tissues, and the heart is faced with the impossible task of raising the blood pressure to normal limits by pumping a decreasing volume of blood through an increasing space resulting from dilated blood vessels. This is irreversible shock, and the patient will die in spite of any treatment.

Death may be caused by interference with the exchange of oxygen and carbon dioxide between the tissues of the body and the outside atmosphere. The term asphyxia is usually used with reference to interference by obstruction of the air passages. Obstruction may be caused by a crushed windpipe or an inhaled pork chop. The air passages may become filled with blood, or the injured person may vomit and then inhale his own vomitus. A crushed chest may prevent normal expansion and contraction of the lungs.

A broken skin surface provides an easy route for invasion by harmful bacteria. Many persons have died of infections which developed in small superficial scratches. In the event of serious injury, the body's resistance to infection is lowered, and the site of abrasion and laceration is potentially far more dangerous than in a person who is otherwise in good health. Pneumonia is almost invariably seen in persons who have survived more than four or five hours after receiving a severe injury.

Sometimes injured persons will die unexpectedly after they have been adequately treated and appear to be recovering. Death in such cases is usually caused by embolism. An embolus is a foreign object traveling from one site to another in the blood stream. These may be blood clots, particles of fat or bone marrow, or air bubbles. Injury to the extremities may result in the formation of clots within the veins. If these break loose, they are immediately carried through the blood stream to the heart and into the lungs. Similarly, globules of fat and bone marrow may escape into the veins from the site of crushed tissues and broken bones. A large clot may cause a massive stimulation of nerve endings in the lungs, these stimuli overwhelming the normal feedback controls between the heart and brain, resulting in instantaneous death. Continuous showers of small clots or fatty material will plug the pulmonary capillaries and cause a slower, asphyxiant type of death.

The medical impact of blunt violence on the human body can be severe. Appearance of such impact is often not visible. This element affects not only medical diagnosis but also legal liability. The necessity of wise medicolegal investigation of incidents suspected to involve blunt violence is most important.

# Now! 2 appetizing foods make serum cholesterol control easier more effective than ever!

# CHLOROMYCETIN®

(chloramphenicol, Parke-Davis)

Wound infection—a common postoperative complication—can very often be traced to staphylococcal invasion.[1-3] In such cases, CHLOROMYCETIN may well be an agent of choice, since "...the very great majority of the so-called resistant staphylococci are susceptible to its action."[4]

Contributing significantly to this preference is the fact that staphylococcal resistance to CHLOROMYCETIN remains surprisingly infrequent, despite widespread use of the drug.[5,6] For example, even though consumption of CHLOROMYCETIN at one hospital increased markedly since 1955, there was little change in the susceptibility of staphylococci to the drug.[6]

Characteristically broad in its range of antibacterial action, CHLOROMYCETIN has also proved valuable in surgical infections caused by other pathogens—both gram-positive *and* gram-negative.[7-8]

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

See package insert for details of administration and dosage.

*Warning:* Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, or viral infections of the throat, or as a prophylactic agent.

*Precautions:* It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.

*References:* (1) Pulaski, E. J., & Taylor, L. W.: *California Med.* 92:35, 1960. (2) Finland, M.: DM: Disease-a-Month, Sept., 1960, p. 3. (3) Monsour, V.; Bernard, H. R., & Cole, W. R.: *Missouri Med.* 57:1006, 1960. (4) Welch, H., in Welch, H., & Finland, M.: Antibiotic Therapy for Staphylococcal Diseases, New York, Medical Encyclopedia, Inc., 1959, p. 14. (5) Bauer, A. W.; Perry, D. M., & Kirby, W. M. M.: *J.A.M.A.* 173:475, 1960. (6) Petersdorf, R. G., *et al.*: *Arch. Int. Med.* 105:398, 1960. (7) Goodier, T. E. W., & Parry, W. R.: *Lancet* 1:356, 1959. (8) Lind, H. E.: *Am. J. Proctol.* 11:392, 1960.

69161

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

# For easier relief of fecal impaction

## FLEET®
## OIL RETENTION ENEMA

*READY-TO-USE SQUEEZE BOTTLE*

When impaction requires fecal softening, Fleet Oil Retention Enema permits easy, rapid administration... without inconvenience or messiness of old-style procedures. Insertion is made safe with pre-lubricated, anatomically correct 2-inch rectal tube.

*Ready-to-Use Squeeze Bottle contains:*
4¼ fl. oz. Mineral Oil U.S.P.

Fleet

*C. B. FLEET CO., INC.*
*Lynchburg, Virginia*


## MEETINGS and Postgraduate Courses

EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA: Postgraduate course in internal medicine, to be held September 25-29. For further information, write to: Dr. J. Willis Hurst, Department of Medicine, Emory University School of Medicine, 69 Butler Street S. E., Atlanta 3.

STATE UNIVERSITY OF IOWA COLLEGE OF MEDICINE, IOWA CITY: Medical postgraduate conferences for 1961 and 1962:

- Pediatrics, September 13-14
- Anesthesiology, September 23-24
- Radiology, October 7
- Arthritis and rheumatism, October 13-14
- Urology, October 13-14
- Otolaryngology and maxillofacial surgery, November 10, December 13 and January 17
- Cardiac diseases, November 17-18
- Respiratory diseases, December 1
- Surgery, December 5-6
- Obstetrics and gynecology, January 9-10
- Refresher course for the general practitioner, February 13-16

For further information, write to: Dr. John Armes Gius, Director, Postgraduate Medical Studies, Office of the Dean, College of Medicine, Iowa City, Iowa.

UNIVERSITY OF CALIFORNIA MEDICAL CENTER, SAN FRANCISCO: Postgraduate courses to be held in 1961 and 1962:

- Symposia in obstetrics and gynecology, September 14-16
- Internal medicine—a selective review, September 18-22
- Psychotherapy in medical practice, Wednesdays, September 20-December 6 and January 31-April 18
- Neuropsychiatry in general practice, Napa State Hospital, Imola, Thursday evenings, September 28-November 2 and February 15-March 29
- A clinic on human disability, Morrison Center for Rehabilitation, September 29-30
- Lectures in medicine, Oakland Hospital, Oakland, Tuesday evenings, October 3-November 28
- Bone: Clinical applications of recent advances, October 7-9
- Urology, October 12-14
- Problems due to infection in medicine and surgery, Franklin Hospital, October 28-29
- Problems of adolescence, Children's Hospital, November 4
- Alcohol and civilization, November 11-13
- Psychiatry in general practice, Napa State Hospital, Imola, November 18-19
- Surgery of the hand and forearm, December 1-3
- External diseases of the eye, December 7-9
- Psychiatric aspects of medical practice, Stockton, December 9-10
- Skin problems in children, Children's Hospital, January 13
- Man and civilization: Control of the mind, part 2. January 27-29
- Dermatology, February 9-10
- Child development, Children's Hospital, March 10
- Diagnostic radiology, March 14-18

For further information, write to: Dr. Seymour M. Farber, Assistant Dean in Charge of Continuing Education, University of California Medical Center, San Francisco.

# Radiology

PAUL C. HODGES*

## X-ray Technic

SOME months ago the Editors of POSTGRADUATE MEDICINE suggested that I present in this column advice to physicians on certain technical phases of x-ray work. It was not intended, I am sure, that I presume to teach "Practical radiography in one easy lesson," any more than it is expected that the monthly exposition of a particular phase of x-ray diagnosis amounts eventually to a complete training in diagnostic radiology. There is a basic difference, however, between the two types of subject matter. All physicians need insight into the data and reasoning back of the conclusions drawn by the radiologists to whom they refer patients if they are to choose such consultants wisely and wisely to employ the information obtained from them. The information, after all, is a part of medicine, an extension of the education which starts in medical school and continues throughout life. However, it is commonplace and, on the whole, desirable that the average modern physician does not employ his time or burden his memory with technical details of radiology. It was not always so.

For nearly a quarter of a century after the discovery of x-rays, there was no such thing as a radiologist. The basis for everything we now know as diagnostic radiology was laid by enthusiastic, talented, hard-working physicians who adapted x-rays to their needs, just as their ancestors had adapted the stethoscope, the fever thermometer, the microscope and the laboratory test tube. Medical practice laws allow duly licensed physicians the widest discretion in deciding which medical procedures to undertake and which ones to consider outside their sphere of competence. However, powerful extralegal factors, such as the cost and difficulty of obtaining malpractice insurance; the approval or disapproval of other physicians in the community; and, most important of all, the basic decency of human beings, induce most physicians to avoid procedures they consider beyond their scope. Few physicians undertake general or special surgery unless they have had serious, prolonged postgraduate surgical instruction. Likewise, in the field of radiology, most physicians agree that only the simpler procedures are permissible unless one has had special training.

However, at this point in the argument, a serious fallacy creeps in, namely, the belief that the general physician has merely to employ a registered technician and accept the presumably enlightened tutelage of a manufacturer's representative in order to enjoy the convenience and financial rewards of performing simple x-ray procedures in his own office. I shall discuss later the fallacy involved in this concept, but, first, let me attempt to disarm

*Emeritus Professor, Department of Radiology, University of Chicago, Chicago, Illinois.

the suspicion that as a radiologist my views are hopelessly prejudiced.

Radiology began to be recognized as a medical specialty a little over 40 years ago, and the American Board of Radiology was established in 1934. Like most of my colleagues in radiology, I feel that patients and their physicians are better off when, as far as possible, all radiologic procedures are in the hands of qualified radiologists. On the other hand, as a teacher in China many decades ago, one of my major activities was to assist physicians in missionary and other hospitals there to add to their surgical and clinical skills the ability to operate simple x-ray equipment and perform the simpler x-ray examinations. From my meager knowledge of the way in which radiology is practiced in rural communities in the United States, I suspect that versatile, intelligent physicians who have the time and the inclination to become high-grade amateurs in the field of diagnostic radiology will do a better job than nonmedical technicians working under the casual supervision of peripatetic, circuit-riding radiologists who "make" the town for a few hours once or twice a week to read films, which they sometimes do late at night or early in the morning when physicians, technicians and the patients concerned are not available for questioning or for further examination.

I suspect that few will question the wisdom of adding knowledge of the simpler phases of diagnostic radiology to the skills of physicians working in areas not properly covered by trained radiologists; however, in a competitive economy, most, if not all, x-ray manufacturers are under pressure to push their equipment among physicians of all sorts and in all locations. I am told that with the recent broadening of the coverage of medical insurance policies in certain states there has been a phenomenal increase of equipment sales to physicians, without regard to their geographical location, individual aptitude, or availability of unencumbered time. This brings us back to the fallacy referred to earlier, namely, the mistaken concept that one has merely to buy equipment and hire a technician in order to be in business.

### *Importance of Paramedical Personnel*

Faithful, competent x-ray technicians and office, floor and operating room nurses deserve and receive the sincere respect and appreciation of the physicians with whom they work. Without such helpers, a physician's special skills can be enjoyed by a mere fraction of the number of patients he normally serves, but without him, the best efforts of such personnel amount to little. He is an essential member and they are extremely valuable members of a team. The best of the manufacturers' representatives can be and frequently are helpful to radiologists and to other physicians who, through enthusiastic application, have made radiologic technic a hobby. These representatives are badly out of their depth, however, when they, along with nonmedical technicians, attempt to supervise the technical work in an office or hospital. To the physician who contemplates or is engaged in diagnostic radiology as a sort of absentee landlord without active personal participation, my advice is, "Do not do it." Those who do actively participate may, I hope, find some help in certain of the following specific suggestions.

I shall refer to the latter physicians as amateur radiologists, implying the prefix "high-grade" and the concept that in approaching the subject as a sport or hobby they have acquired technical proficiency approaching that of professionals.

### *Fluoroscopy*

In spite of its simplicity, convenience and low cost of operation, the fluoroscope no longer should be used except by the specialist, and he should use it only when filming alone will not suffice. Most commercial fluoroscopes are grossly dangerous to patient and operator alike, and, even under the very best of conditions (conditions almost never realized), radiation doses are 10 times or more as great as those required for the making of even large numbers of films.

Image amplifiers, of which so much was expected a decade ago, have proved valuable in certain special respects but fail in one important particular, namely, the large-scale re-

duction of the dose required for fluoroscopic examination of the chest or, particularly, the alimentary tract. They are, in addition, very expensive and require expert maintenance.

Routine fluoroscopy of the chest, particularly in children, should be abandoned completely, and fluoroscopy incident to diagnosing lesions of the central nervous system, the cardiovascular system and the alimentary tract should be deferred until the patient is in the institution in which any indicated surgery is to be done. Preliminary examinations of this sort conducted elsewhere are almost certain to be repeated in the institution to which the patient is taken for surgery, with resulting needless increase in the radiation dose to his tissues.

### *Filming Apparatus*

Many of the states are adopting regulations relative to the registration and, in some cases, the licensing of diagnostic x-ray apparatus, but it is beyond the scope of this column to advise in detail how to comply with these regulations and avoid unwitting violation of newly enacted laws. In general, compliance with the recommendations of handbooks[1,2] will suffice, and in all of our larger cities there are professional radiation physicists who, for a fee, will survey and certify x-ray installations. As Trout, Kelley and Lucas[3] pointed out, diagnostic installations frequently can take advantage of the density of ordinary building materials and avoid expensive leading of walls. It is of the greatest importance to arrange apparatus so that the primary beam is restricted to outside walls and to thick concrete floors.

### *Old Versus New Equipment*

From time to time, one hears the suggestion that laws should prohibit the use of x-ray equipment older than, say, 10 years. Of course, this is in keeping with the alleged current concept of built-in obsolescence, but otherwise it is pure foolishness. Certainly, much old equipment was inadequately protected, and at least some of that currently produced is better in that respect; however, a competent serviceman can improve shielding where necessary, and the "proof of the pudding" is in the radiation physicist's survey, which is essential whether equipment is old or new. It so happens that certain equipment which we are using today in our laboratory is more than 25 years old, but it is better from the standpoint of radiologic safety than any modern equipment with which I am familiar.

### *Films of Skull, Chest, Trunk and Extremities*

All x-ray examinations of the skull, chest, trunk and extremities are within the scope of the amateur radiologist as I have defined him. All should be made using cassettes and fast screens, and, in my opinion, all except those of the extremities should be made with stationary 8 to 1 or 12 to 1 grids. I believe that the improved bone detail in extremity roentgenograms made on "nonscreen" film is of little clinical advantage when weighed against increased dose and the inconvenience of multiple-film types.

*Restriction of primary beam*—Without exception, tube ports or cones should be rectangular rather than circular, and care should be exercised to assure a rectangular beam barely large enough to cover the film. Particularly in children, exposure should be limited to the smallest-possible body area.

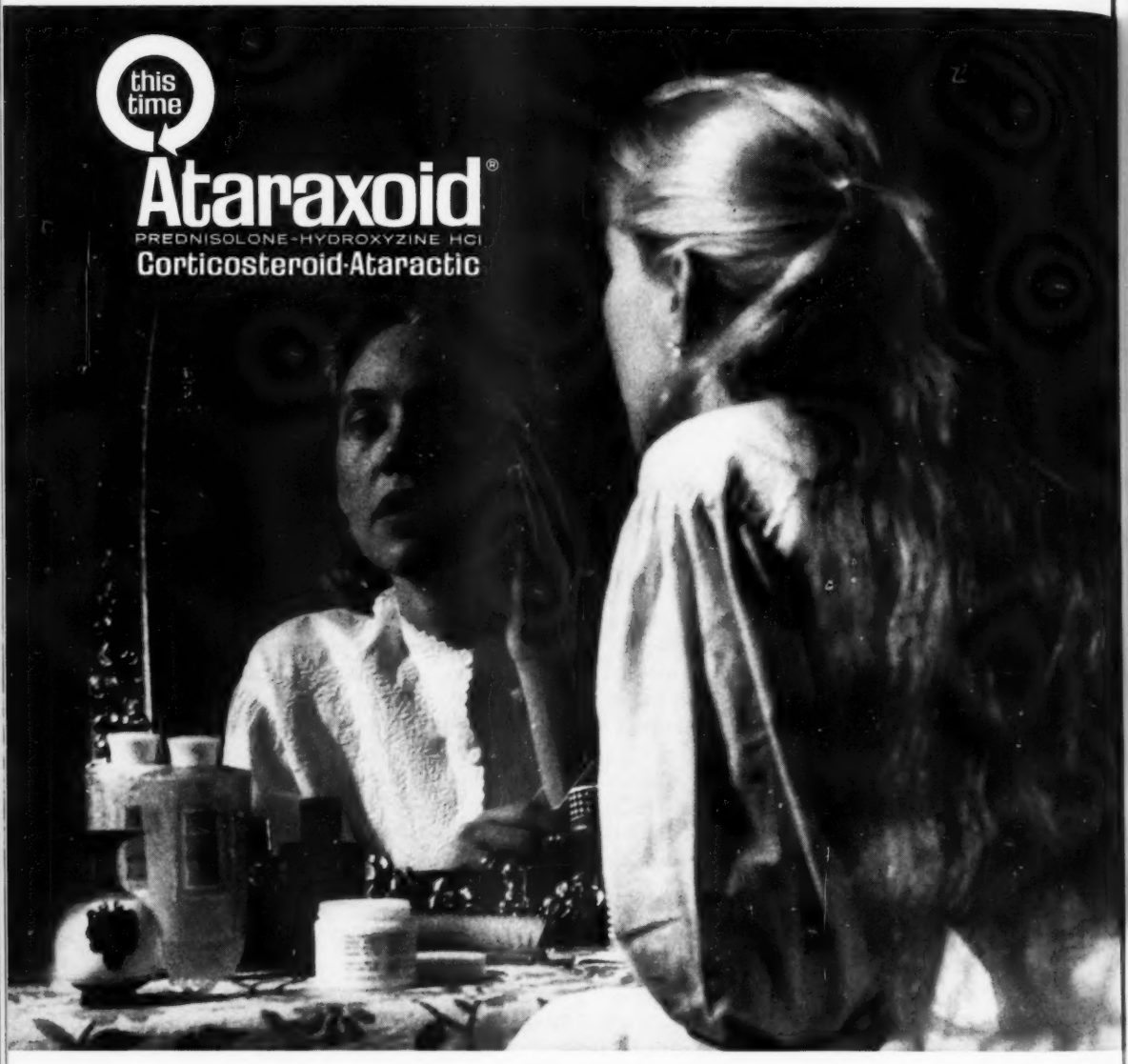
*Added filter*—A 2 mm. aluminum filter should be permanently mounted in the ports of all diagnostic x-ray tubes.

*Focal spot size in rotating anode x-ray tubes*—Twin, 1.5 mm. focal spots are preferable to one that is larger and one that is smaller than this size. The 1.5 mm. focal spot is large enough and small enough for all practical purposes of the amateur radiologist, and, when twin filaments are used, one is available when the other has burned out. Manufacturers of x-ray tubes assure me that it is not filament life that limits the life of x-ray tubes, but my experience has been quite otherwise.

*Darkroom*—When x-ray films are good or bad, the explanation frequently lies in the darkroom rather than in the exposing room, and here the physician who happens to be an experienced photographer will have an

*(Continued on page A-63)*

# when anxiety intensifies allergic dermatose




## for more effective treatment of allergic disorders

*"Excellent results were obtained with the prednisolone-hydroxyzine combination in a greater proportion of patients (75.6 per cent) than with prednisolone alone (48.3 per cent)."*[1]

**ATARAXOID IN BRIEF** ATARAXOID contains the glucocorticoid, prednisolone, and the ataractic agent, hydroxyzine. **ADVANTAGES:** ATARAXOID combines the tension-relieving effects of hydroxyzine with the anti-inflammatory action of prednisolone, a well-established corticosteroid, for superior control without *unexpected* side effects. Owing to the lessening of the anxiety component, there is often an enhanced response to prednisolone, permitting significant reduction in the steroid dosage required to provide relief. **INDICATIONS:** Those conditions amenable to steroid therapy in which anxiety and other emotional factors are associated; allergic/inflammatory diseases of the skin and eyes, chronic bronchial asthma, severe hay fever, and other allergic states; rheumatoid arthritis; collagen diseases and related conditions; and other musculoskeletal disorders (myositis, fibrositis, bursitis, etc.). **ADMINISTRATION AND DOSAGE:** ATARAXOID dosage varies with individual response. Clinical experience suggests the following daily dosage: *Initial therapy*—4-6 ATARAXOID *5.0* Tablets. *Maintenance*—1-4 ATARAXOID *5.0* Tablets or 2-8 ATARAXOID *2.5* Tablets. After initial suppressive therapy, gradual reduction of prednisolone dosage should begin and continue until the smallest effective dose is reached. Prescribe in divided doses, after meals and at bedtime. **SIDE EFFECTS:** Prednisolone may produce all of the side effects common to other corticosteroids. As with other corticosteroids, insomnia, mild hirsutism, moonface and sodium retention have occurred. Osteoporosis may develop after long-term corticosteroid therapy. **PRECAUTIONS AND CONTRAINDICATIONS:** Usual corticosteroid precautions should be observed. Incidence of peptic ulcer may increase on long-term prednisolone therapy. However, therapy has often been maintained for long periods without adverse effects. Contraindicated in infectious disease including active tuberculosis (except under close supervision), peptic ulcer, certain infections of the cornea, such as dendritic keratitis, superficial punctate keratitis, epidemic keratoconjunctivitis, and in patients with emotional instability. Caution is indicated in the treatment of diabetic patients and patients with severe cardiovascular disease, and in some cases sodium restriction and potassium supplementation must be considered. **SUPPLIED:** As green, scored ATARAXOID *5.0* Tablets, containing 5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride and blue, scored ATARAXOID *2.5* Tablets, containing 2.5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride.

*More detailed professional information available on request.*

1. Brown, E. B., and Seideman, T.: J. Allergy 29:80, Jan., 1958.

*Science for the world's well-being®* Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc. New York 17, N.Y.



advantage over those who must depend on others. Modern x-ray film exposed with intensifying screens has enormous latitude, which makes possible the unwise practice of overexposing films and then developing them just long enough to obtain a reasonably good image. Vastly better is the practice of establishing rigid control of strength and temperature of solutions, developing to the full time stipulated by the film manufacturer, and then, by trial and error, determining the proper conditions of time, kilovoltage and milliamperage for anatomic parts of various thicknesses. Adherence to these standards will assure minimal tissue doses to patients and employ film latitude as a compensator for unanticipated tissue thickness and density rather than as an antidote for carelessness. Automatic film processors are mandatory for large installations, but the small, relatively inexpensive types of processors introduced very recently eventually may become cheap enough to be used even by the amateur radiologist.

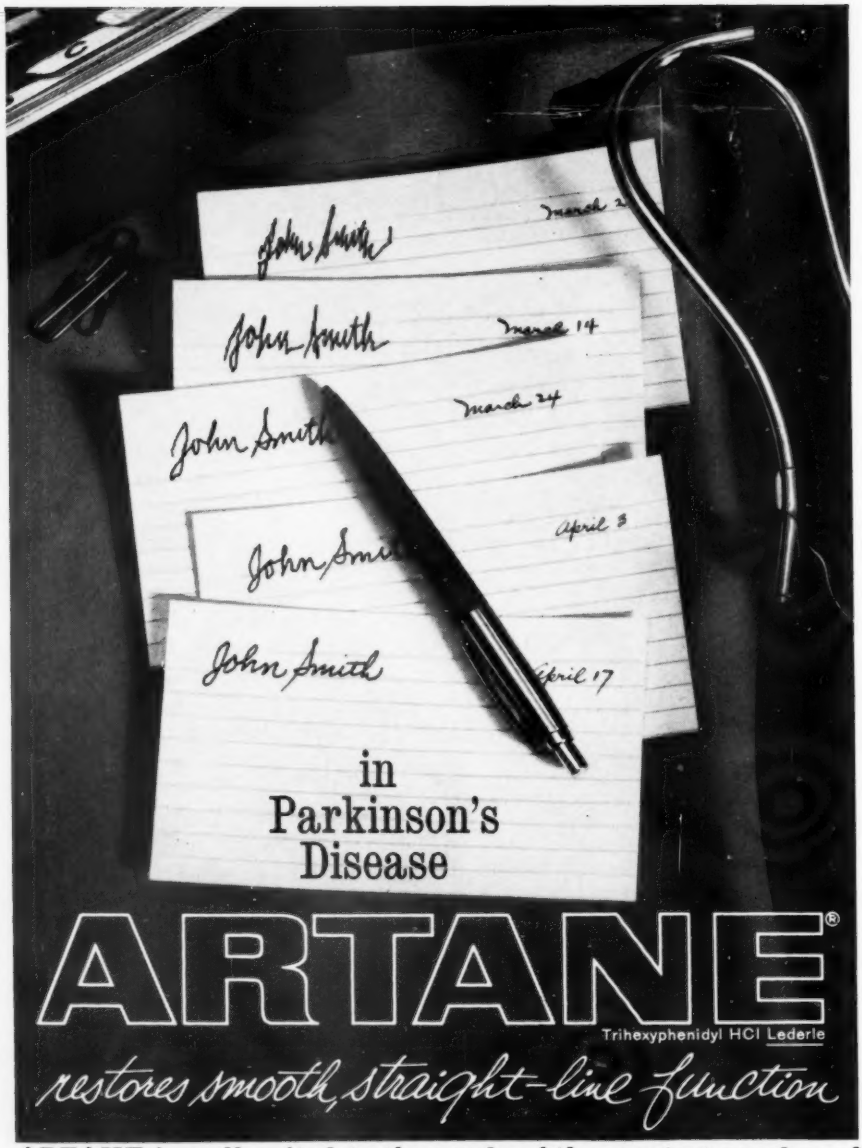
*Gonadal shielding*—By sharp, rectangular coning of the beam and direct shielding of the testes in men,[4] it is possible to decrease substantially the gonadal dose in filming of such parts as the urinary tract, pelvis and hips.

### *Comment*

Physicians who are situated where a professional radiologist is not easily available, who have the free time and the inclination to master a few technical details, and who are blessed with the help of technicians who will work with them rather than for them can do a surprisingly good job for their patients in many of the simpler phases of diagnostic radiology. They also are apt to find in the work something of the relaxation others find in color photography, cabinet making, or golf.

REFERENCES

1. Medical X-ray Protection Up to Three Million Volts. Handbook No. 76. Bureau of Standards (February 9) 1961.
2. SCHULZ, R. J.: A Primer of Radiation Protection. New York, General Aniline and Film Corp., 1961.
3. TROUT, E. D., KELLEY, J. P. and LUCAS, A. C.: Conventional building materials as protective radiation barriers. Radiology 76:237 (February) 1961.
4. HODGES, P. C., STRANDJORD, N. M. and MCCREA, A.: A testicular shield. J.A.M.A. 167:1239, 1958.




**ARTANE** is well suited to the needs of the greatest number of patients.[2] Improves rigidity, akinesia and mental depression. Controls oculogyria . . . remarkably free of toxic reactions.[1]

Indicated: All types of Parkinsonism, and to control extrapyramidal reactions in ataractic therapy. Supplied: Tablets, 2 mg. and 5 mg.; Elixir, 2 mg./5 cc. tsp. 1. Constable, K.: J. Am. M. Women's A. 15:757 (Aug.) 1960. 2. Critchley, M.: Brit. M. J. 2:1214 (Nov. 15) 1958.

*Request complete information on indications, dosage, precautions and contraindications from your Lederle Representative or write to Medical Advisory Department.*

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

# Medicine from Abroad

*FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS*


ARGENTINA: ISAAC BERCONSKY, M.D.
AUSTRALIA: GRAYTON BROWN, M.D.
AUSTRIA: M. ARTHUR KLINE, M.D.
BRAZIL: A. BRICKMANN, M.D.
DENMARK: TORBEN JERSILD, M.D.
ENGLAND: R. SCOTT STEVENSON, M.D.
FRANCE: JEAN MEYER, M.D.
GREECE: NICK J. PHOTINOPOULOS, M.D.
ISRAEL: RAFAEL J. SCHEN, M.B.
JAPAN: HARUTO UCHINO, M.D.
SPAIN: MRS. EDITH BULSON
U.S.S.R.: ANATOLY S. RABEN, M.D.


## AUSTRIA

***Pediatric endocrinology***—In a lecture to the Austrian Physician's Society at Vienna, Dr. W. Swoboda reported on the children with endocrine disorders seen at the University Pediatric Clinic of Vienna during the past three years. The majority of the cases involved disorders of the thyroid gland, particularly all types of goiter and disturbances of growth. Dr. Swoboda noted that the disturbances of growth occurred in a particularly heterogeneous group of patients.

Dr. Swoboda described his investigation of a large series of children with congenital hyperfunction of the thyroid and of a smaller series of children in whom hyperfunction was associated with cancer of the thyroid. He also considered problems of intersex. In discussing diagnosis and therapy, he emphasized the adrenogenital syndrome and dysgenesis of the gonads. The adrenogenital syndrome caused by carcinoma of the suprarenal gland was present in two girls in his series. One patient died from metastases. The tumor in the other patient was removed, and now, three years after the operation, cure is considered to be almost complete.

Dr. G. Geyer remarked that most cases of carcinoma of the suprarenal gland are not as favorable for operation as was the case discussed by Dr. Swoboda. Usually, metastases will occur after removal of the tumor, and there will be continued growth of malignant tumors. The clinical picture will be that of virilism or a form of Cushing's syndrome.

Dr. Geyer stated that o,p-DDD, a derivative of the insecticide DDD, has been used recently in treating carcinoma of the suprarenal gland. This agent inhibits production of steroids by the normal suprarenal gland and the hormone-producing tumors. An "endocrinic remission" was achieved in 20 of 30 patients treated with o,p-DDD. In one-third of the patients there was marked regression of the metastases from the tumor and necrotic degeneration of the tumor tissue. At the University Clinic of Medicine, administration of o,p-DDD to a patient for more than two months produced marked endocrinic remission but did not effect any reduction detectable by palpation in the size of a metastatic nodule of the tumor.

Dr. R. Wegner discussed the incidence of congenital heart defects in patients with gargoylism. Although there are many references in the literature to congenital heart defects in association with gargoylism, none of the patients with congenital heart defects seen at the University Clinic of Medicine had gargoylism. Dr. Swoboda said

*(Continued on page A-70)*

that true congenital heart defects are rare in cases of gargoylism.

## ENGLAND

***Psychiatric consequences of gastrectomy***—Compared with most of his colleagues, the psychiatrist sees many patients who date their symptoms from the time of an operation. Women in whom intractable neurotic illness develops after a hysterectomy are seen fairly frequently in psychiatric outpatient departments. However, surprisingly little has been written on the psychiatric sequelae of partial gastrectomy and other surgical procedures for relieving peptic ulcer. European workers seem more familiar with this problem (particularly when alcoholism is involved) than do the American and British.

In the *British Medical Journal,* Dr. F. A. Whitlock, psychiatrist, Newcastle General Hospital, has reviewed a series of 25 patients with psychiatric complications following partial gastrectomy. Evidence cited suggested that the personality of the patient with duodenal ulceration differs from that of the patient with gastric ulceration. In this series, all the alcoholics and drug addicts had had surgery to relieve symptoms of duodenal ulcer. Although the surgery relieved pain, dumping syndromes developed in these patients, adding to their discomfort and leading to increased consumption of alcohol or drugs for relief.

Dr. Whitlock stated that it is difficult to prevent symptoms of the kind described. The surgeon must decide whether or not to operate on a patient with a duodenal ulcer who is known to be a moderate drinker and who has had a number of acute complications from his ulcer. If he does not operate, the patient's life may be endangered; if he performs a partial gastrectomy, a reasonably adjusted individual may be converted into a chronic alcoholic incapable of working and become a burden to himself and his family. Dr. Whitlock believes that those patients who show psychopathic features or are prone to resort to alcohol to relieve their anxieties should be detected before surgery. Psychiatric treatment could be started then and continued after the operation.

## FRANCE

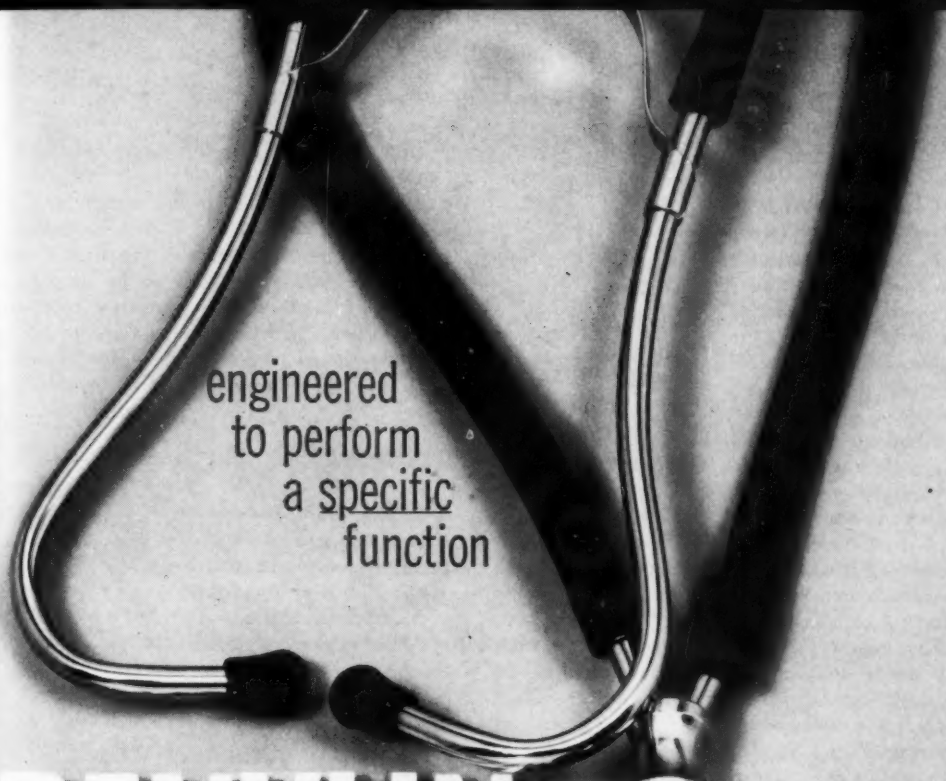
***Tuberculous meningitis***—Dr. Guy Godlewski has presented a study of 3,667 patients with tuberculous meningitis in the *Bulletin de l'Académie nationale de médecine.* Most of these patients were observed between 1950 and 1953. Since that time, the incidence of tuberculous meningitis has decreased by three-fourths. Between 1948 and 1959, six patients per thousand were hospitalized with this disease. It occurs primarily in children less than 15 years old, and one-third of these patients are less than two years old. Recrudescence of tuberculous meningitis appears in patients between the ages of 20 and 30 but rarely in those more than 50.

The treatment of choice is administration of a combination of streptomycin and isoniazid for four months, followed by isoniazid and PAS for 18 months. Most French general practitioners administer the medication by intraspinal injection only in severe cases. Corticoids are used for a few weeks only. These agents cause acute episodes to subside rapidly, minimize the possibility of recurrence, and reduce the number of sequelae; however, most physicians agree that they do not improve the prognosis. Systematic use of BCG vaccine has proved very effective. According to Professor Despierres, not one case of tuberculous meningitis was observed among 100,000 children of Lyons who were vaccinated with BCG. Professor Etienne Bernard noted that 150 children who died of this disease in 1959 had not been vaccinated with BCG.

Treatment must be started early; the mortality is doubled if the disease is untreated for a week, and it is tripled if treatment is delayed much longer. In military hospitals, in which patients are hospitalized early in the course of the disease and are closely watched, the mortality from tuberculous meningitis is only 6 per cent.

The prognosis for patients with this disease is improving. The survival rate for infants has risen within a few years from 18 to 64 per cent; for children more than two years old, it has increased from 45 to 89 per cent; and for adults, it has improved from 36 to 83 per cent. Between 20 and 30 per cent of the surviving patients will have neurologic sequelae.

*(Continued on page A-72)*




# BENYLIN EXPECTORANT

## specifically designed to help control cough

Just as a medical instrument is engineered for maximum efficiency in performing its specific function, BENYLIN® EXPECTORANT is formulated to provide effective relief of cough associated with colds or allergy.

The outstanding antitussive action of BENYLIN EXPECTORANT is attributed to a combination of carefully selected therapeutic agents. Benadryl,® a potent antihistaminic-antispasmodic, reduces bronchial spasm, quiets the cough reflex, and lessens nasal stuffiness, sneezing, lacrimation, itching, and other allergic manifestations. Concurrent respiratory congestion is relieved by expectorant agents that efficiently break down tenacious mucosal secretions. In addition, a demulcent action soothes irritated throat membranes. 59061

BENYLIN EXPECTORANT is a pleasant-tasting, raspberry-flavored syrup...completely acceptable to patients of all ages.

**supplied:** BENYLIN EXPECTORANT is available in 16-ounce and 1-gallon bottles.

Each fluidounce contains: 80 mg. Benadryl Hydrochloride (diphenhydramine hydrochloride, Parke-Davis); 12 gr. ammonium chloride; 5 gr. sodium citrate; 2 gr. chloroform; 1/10 gr. menthol; and 5% alcohol. *Indications:* Relief of coughs due to colds, other symptoms associated with colds, and coughs of allergic origin. *Dosage:* Adults—1 to 2 teaspoonfuls every three to four hours. Children—½ to 1 teaspoonful every four hours. *Precautions:* Products containing Benadryl should be used cautiously with hypnotics or other sedatives; if atropine-like effects are undesirable; or if the patient engages in activities requiring alertness or rapid, accurate response (such as driving).

**PARKE-DAVIS**

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

## JAPAN

***Causes of death in hypertensive patients***—In order to determine the most common causes of death in hypertensive patients in Japan, the Committee on Visceral Circulation conducted a statistical survey of 1,472 patients with essential, including malignant, hypertension observed during the period from 1951 to 1956. These patients had a systolic blood pressure above 150 or a diastolic blood pressure above 90 mm. of mercury. Patients with hypertension due to renal, endocrine, neurogenic or other definite causes were not included in the study.

The majority of the subjects selected were patients in the hospitals or infirmaries of 10 medical schools; some were outpatients. Diagnosis was established clinically in 732 cases and at autopsy in 740. The causes of death were classified as direct, indirect (provoking the direct cause), and accessory (contributing to the direct cause).

The study showed that the incidence of cerebral, cardiac or renal involvement as the direct cause of death was higher in the clinically diagnosed cases than in those diagnosed at autopsy. However, these complications occurred in this order of frequency in both groups. In the cases diagnosed at autopsy, the combined incidence of vascular involvement as the direct cause of death was different in each age group, decreasing with age. The incidence of other causes of death, especially pneumonia, increased markedly in patients more than 60 years old. Cerebral lesions caused the death of 34.4 per cent of patients in the fourth and fifth decades of life and 20.9 per cent of those more than 60. The mortality from cardiac lesions increased with age. In both the clinically diagnosed cases and those diagnosed at autopsy, renal involvement was the most common direct cause of death in the group less than 40 years old.

Vascular involvement was a contributing factor in the death of 61.1 per cent of all patients. It was the direct cause of death in 48.5 per cent of the cases diagnosed at autopsy, and played a significant role as an indirect or accessory cause of death, particularly in the aged. Cerebral and renal lesions were found more frequently as the systolic or diastolic blood pressure became more elevated.

When the findings in the eyegrounds were above grade 3, according to the Keith-Wagner classification, the incidence of renal involvement as the direct cause of death was increased. As the systolic or diastolic blood pressure rose, especially in patients with severe changes in the eyegrounds, the incidence of renal involvement as the indirect cause of death also increased.

## SPAIN

***Kidney transplants***—In a paper on kidney transplants, read before the Medico-Surgical Academy of Madrid, Dr. Alfonso de la Peña concluded that such transplants are practicable; however, the morbidity and mortality are great, and the procedure is possible only between univitelline twins who are absolutely identical. Even in these cases, there is a possibility of evolutionary lesions if the connections undergo stenotic processes or if the same disease recurs. Therefore, the definite value of a transplant cannot be demonstrated for a period of years.

Up to the present time, kidney grafts between persons other than twins have yielded negative results. The kidney disintegrates, the graft does not take, and the patients die from histologic conflicts, irrigation defects, the consequences of surgical errors or accidents, permeable vascular sutures, thrombosis, stenosis, etc.

Two kidney transplants have been performed in Madrid. One, between 29 year old univitelline twins, was performed by a physician who had made experimental studies of renal transplants for several years. The other transplant was from a progenitor to an offspring. In both cases, the patients died immediately.

Because an incurable kidney lesion involves so much suffering for the patient and his family, there is an urgent need for a trustworthy and unequivocal medical opinion regarding treatment. It is to be hoped that in the future the prognosis in kidney transplants will be improved through avoidance of allergic and septic conditions which annul the graft, development of more accurate technics in vascular surgery, and a better understanding of humoral homeostasis.

# Auto-immune Disease: Some General Principles

FRANK MACFARLANE BURNET*

*The Walter and Eliza Hall Institute of Medical Research, Melbourne*

*Four central concepts are presented which may be helpful for the understanding of auto-immune disease:*

*1. The immune status of the body is a manifestation of the population dynamics of lymphoid cells which are immunologically competent.*

*2. The existence of a mechanism of immunologic homeostasis ensures the maintenance of full tolerance for all normal body components.*

*3. Auto-immune disease is a result of the emergence of "forbidden clones" that for one reason or another find it possible to transgress the normal rule and react damagingly with body constituents.*

*4. Circulating antibody is regarded primarily as an index of the presence of corresponding immunologically competent cells. It is neither necessarily nor in most cases probably the actual pathogenic agent in auto-immune disease.*

At the present time there is acute interest among physicians in those diseases which in whole or in part result from a misdirected immunologic attack on some of the body's own components. Auto-immune disease may be provisionally defined as any condition associated with damaging interaction of immunologically active cells or antibodies on normal components of the body. In accordance with the spirit of the times, the approach has been very much at the laboratory level and has been largely centered on the estimation of antibodies against cellular antigens (auto-antibodies) in patients' serum. A special stimulus has been provided by the clear-cut demonstration (by Roitt and associates[1] in 1956 and Belyavin and Trotter[2] in 1959) that Hashimoto's disease of the thyroid is regularly associated with high-titer antibodies against at least two organ-specific antigens and can be closely imitated in experimental animals by the injection of organ extracts plus Freund's adjuvant.

Along with clinical and experimental study, there is need or at least justification for seeking a theoretical basis for the processes concerned in auto-immune disease. Without working hypotheses, clinical and experimental investigations tend to be sterile, and even a highly speculative approach may have virtues

*Director, The Walter and Eliza Hall Institute of Medical Research, and Professor of Experimental Medicine, University of Melbourne, Melbourne, Australia; 1960 Nobel prize winner in Medicine.

in suggesting ways in which we can usefully intervene at a practical level. This is my only justification for presenting what is a frankly personal and speculative approach to these problems.

### *The Basic Immunologic Processes*

We are concerned with what might almost be called the new immunology—not with the reactions of the body in defending itself against microorganismal invasion but with an altogether subtler process. Every multicellular organism, including man, is a highly complex functional mechanism which must maintain its chemical and structural integrity despite an incessant activity in rebuilding and replacing cells and macromolecules. In all biologic processes there are possibilities of error, and the organism must possess a wide range of homeostatic mechanisms at both metabolic and cellular levels. It has been almost the rule that the first evidence of the existence of a homeostatic mechanism has been derived from pathologic phenomena. Perhaps the central theme of this paper is that auto-immune disease must represent essentially the failure of a homeostatic mechanism, and this theme may provide the best approach to the understanding of that mechanism.

Immune reactions, cellular or humoral, are based on the existence of mesenchymal cells, particularly of the lymphocytic and plasma cell series, which, because of their capacity to react in one way or another with a particular antigen pattern, can be termed immunologically competent (I.C.) cells. There is abundant controversy as to how I.C. cells arise in the first place, but, accepting their existence, we are on firm ground in saying that the immunologic status of the body depends on the number and distribution of the various clones of I.C. cells which make up part or perhaps all of the lymphoid cell population. The normal call to activity, whether for the proliferation of a given line of cells or for the synthesis and release of antibody, is renewed contact with the corresponding antigen. Immunity is essentially a matter of the population dynamics of lymphoid cells.[3]

Without attempting to discuss here the way by which the situation may develop, we are forced to accept the fact that in the normal mammalian body I.C. cells whose specificity is directed against body components either do not occur or give no evidence of their existence. For a variety of reasons, we can be almost equally confident that their absence is due to the constant functioning of a mechanism of *immunologic homeostasis*. It is immaterial to the argument as to what precise form that mechanism takes but it is reasonable to assume that it depends on the fact that at some stage in the process by which an I.C. cell is stimulated by antigen to proliferate, continuing presence of or renewed contact with the antigen will inhibit or annul the process. This is in agreement with a variety of findings which relate to both tolerance and immune paralysis.

The possibilities of failure in such a mechanism can be visualized as depending on either (1) the emergence by mutation or otherwise of a cell or clone of cells unresponsive to inhibition by excess antigen or (2) a weakness of the homeostatic mechanism depending on some change in the internal environment where it is normally exercised. This might result either from genetically determined influences or by the impact of an environmental factor.

Irrespective of how the homeostatic mechanism is at fault, the effective result is the emergence into activity of a "forbidden clone." This is a convenient name for any population of I.C. cells directed against an antigenic pattern carried by a body component. The full theoretical development of this concept based on the clonal selection theory of immunity would be inappropriate here, and the reader is referred elsewhere.[4] Such discussion can be bypassed, however, if we accept two main categories of forbidden clones. The first is characterized by an unresponsiveness to normal homeostatic control, resembling in many ways the unresponsiveness of the cells in conditioned malignancies. There is a variety of semimalignant conditions of lymphoid tissues which either have close analogies to auto-immune disease (e.g., multiple myeloma, Waldenström's macroglobulinemia) or are very commonly associated with auto-immune

episodes such as hemolytic anemia (lymphatic leukemia may be cited as a specific example). Presumably such changes represent limited somatic mutation, but the likelihood of such mutation might well be controlled by genetic factors in the usual sense, i.e., involving the germinal cells.

The second possibility for the emergence of forbidden clones can be exemplified by one theory of the pathogenesis of rheumatic fever. This postulates that the tonsillar-pharyngeal lymphoid tissue is a major source of I.C. cells. When there is an association of some hereditary factor or factors with a subacute streptococcal infection, some commonly arising forbidden clones are shielded from inhibition or destruction at the vulnerable phase of their development into reactive cells. Subsequently they can move to other parts of the body when they have outgrown the vulnerable phase.

### *Pathogenic Potentialities of I.C. Cells and Antibodies*

If auto-immune disease exists, we must accept the actual or potential pathogenicity of immunologically competent cells or antibodies, or both. It is important, therefore, to obtain as clear ideas as possible in regard to such pathogenic actions. As yet there are no direct ways of demonstrating the pathogenic action of I.C. cells, and it is advisable to start with the experimental use of anti-organ serums. When an antiserum against rat-kidney extracts is prepared in a rabbit, this serum administered to a rat will provoke a well-marked nephritis. An antiserum against guinea-pig platelets prepared in the rabbit will produce purpura when injected into a guinea pig, and cytotoxic antiserums against a variety of cell lines, which will act vigorously on cells in tissue culture, can be prepared by appropriate immunization of alien species.

Evidence that antibodies produced in an animal against a component of its own cells can be pathogenic in that animal has not yet been provided, and from the nature of the problem it may always be impossible to establish the relative roles of cells and antibody in such circumstances.

There are several examples available indicating that pathogenic effects can be produced by immunization with tissue extracts, notably the production of allergic encephalomyelitis in rats. No one has succeeded in producing this syndrome in another rat by transfer of serum. It can be done, however, by transfer of lymph node cells provided the recipients have been made tolerant to spleen cells of the eventual donor (Paterson,[5] 1960). This does not, of course, exclude the possibility that an antibody produced by the transferred cells is the actual pathogenic agent. A general consideration of the whole field of homograft immunity, delayed hypersensitivity and experimental auto-immune disease, however, points strongly to the predominant or exclusive role of cells rather than antibody in producing all the types of cellular damage shown in these reactions. The demonstration by Algire and associates[6] in 1954 that homografts could persist if they were separated from the host tissues by a membrane permeable to proteins but not to cells is rightly given much weight in this connection.

In auto-immune disease as seen clinically, it is notorious that the available tests for auto-antibodies give highly variable results that are by no means clearly correlated with the intensity of the pathologic changes. Our general conclusion has been that while "auto-antibody" tests are most valuable in establishing the existence of an auto-immune process, they are best regarded not as a measure of a pathogenic agent but as an index of the presence and activity within the body of forbidden clones of I.C. cells. Provisionally at least, the pathogenic activity is best ascribed to the cells themselves.

### *Action of Anti-inflammatory Corticosteroids*

Without any really adequate experimental basis for the belief, any immediate benefit from the therapeutic use of one of the standard corticosteroids is nowadays regarded as a presumptive indication that the condition benefited has an auto-immune component. Among the various actions of cortisone and its derivatives that have been described, the

destructive influence on the lymphocyte in vivo is one of the most clearly defined. It may be related directly to the lymphocytolytic effect, or it may be related to the fact that the corticosteroid drugs have what may be described as a general inhibitory or damping effect on any immunologic reaction involving cell surfaces. If symptomatic benefit follows the damping down of an immune response that is not clearly related to some extrinsic antigen, then it is an obvious deduction that the immune reaction is directed against some component of the body.

### *Significance of Accumulations of Lymphoid Cells*

All the accepted forms of auto-immune disease are associated with accumulations of lymphoid cells in the affected organ or tissue. So, of course, are many chronic infections like tuberculosis and lymphogranuloma inguinale, and it is accepted teaching that any form of chronic irritation is likely to call out a lymphocytic exudate in the vicinity. If it is correct that lymphocytes are to a large extent or wholly immunologically competent cells, then it seems to be a reasonable maxim that wherever lymphocytes are accumulated, and especially if plasma cells are present, an immunologic reason for their being there should be sought. If there is no evidence of bacterial or viral infection, the possibility of an auto-immune condition must come to mind.

### *General Patterns of Auto-immune Disease*

If we accept the concept of the emergence of forbidden clones of I.C. cells as being primarily responsible for auto-immune disease, we have a basis on which to differentiate the patterns seen clinically. If they have arisen because of some environmentally induced modification of the homeostatic process in one of the significant areas of lymphoid cell production or development, then the process should vanish with removal of the environmental factor. The two examples of such *transitory auto-immune disease* which immediately come to mind are rheumatic fever and the benign acquired hemolytic anemia that follows a proportion of attacks of infectious mononucleosis and primary atypical pneumonia. Here we can postulate that infection involving a significant fraction of lymphoid tissue has so modified the local internal environment as to protect certain forbidden clones from being inhibited as they normally would be at some vulnerable stage in their development.

At the other extreme is the *progressive "malignant" auto-immune disease*, of which typical systemic lupus erythematosus is the prototype. In its fully developed form, it is nearly always fatal in a few years. For many patients, however, much can be done to give increased years of survival by the use of large doses of cortisone or its equivalents. The behavior of the more severe cases of this disease is what would be expected if a clone or clones of I.C. cells emerged highly resistant to homeostatic control and capable of giving rise to a wide range of subclones with a variety of specific reactivity. From our present point of view it is immaterial whether such subclones are produced (instructively) by the various potential body antigens or, as we would prefer to believe, by a process essentially of random somatic mutation. What is necessary is that once in existence such clones are stimulated to multiply by antigenic contact in the body and give rise to the concentrations of I.C. cells or antibodies that are responsible for the pathologic changes which are characteristic of the disease.

Between these two extremes is a wide variety of intermediate conditions in which characteristically the disease persists with relapses and remissions over considerable periods and often either is "cured" or goes into permanent remission. Rheumatoid arthritis, discoid lupus, acquired hemolytic anemia, and thrombopenic purpura of auto-immune type may be mentioned. In all these conditions we can visualize the appearance of forbidden clones of lower "aggressiveness" than those of systemic lupus erythematosus and without the full conditioned malignancy of multiple myeloma and leukemia. They will be subject to variably effective homeostatic mechanisms and will be influenced greatly by the distribu-

tion and accessibility of the antigenic determinants involved and by only dimly understood conditions like the relative activity of associated antibody in helping or inhibiting the pathogenicity of I.C. cells. This gives us a general approach toward an understanding of the protean character of auto-immune disease, varying not only in intensity and in course but also in the organs or systems predominantly involved.

### *Auto-immune Conditions in Relation to "Inaccessible" Antigens*

The most intensively studied of the auto-immune diseases in recent years has been Hashimoto's disease of the thyroid, largely because of the ease with which thyroid-specific antibodies can be recognized in the serum. In the classic condition the thyroid is heavily infiltrated with lymphocytes and plasma cells and there are abundant antibodies against thyroglobulin and a cytoplasmic thyroid component in circulation. The orthodox view is probably that the antigens concerned are normally so inaccessible, so secluded from the normal commerce of the body, that no tolerance is developed against them. When for any reason they leak into the circulation, they are treated as foreign antigens and antibody production takes place. This fits well with the finding that such antibodies frequently are found in a variety of thyroid conditions, especially thyrotoxicosis, where there is otherwise no suspicion of auto-immune disease. Hashimoto's disease has, in addition, a much more concentrated incidence in the female sex and a characteristic cellular invasion of the gland by lymphoid cells, which usually goes on to almost complete functional destruction of the gland. Both these features suggest that an additional quality analogous to what is concerned in other auto-immune diseases is needed. This presumably is the same requirement that for an I.C. clone to flourish in the presence of high concentrations of antigen—in the tissue of the thyroid itself in particular—a new quality of the cells is needed which may be called either a heightened aggressiveness or an unresponsiveness to inhibition by the normal homeostatic mechanisms. It remains to be established whether similar principles hold for idiopathic Addison's disease and Sjögren's disease; presumably they do. Until a more acceptable etiology can be provided, the possibility will remain that multiple sclerosis is another auto-immune disease involving an inaccessible antigen or set of antigens. Studies on experimental allergic encephalomyelitis and the similar human cases that have followed immunization with vaccines containing nervous tissue have shown that demyelinating processes can be induced immunologically. The resemblance to multiple sclerosis is, however, rather distant.

REFERENCES


1. Roitt, I. M., Doniach, D., Campbell, P. N. and Hudson, R. V.: Auto-antibodies in Hashimoto's disease (lymphadenoid goitre); preliminary communication. Lancet 2:820 (October 20) 1956.
2. Belyavin, G. and Trotter, W. R.: Investigations of thyroid antigens reacting with Hashimoto sera; evidence for an antigen other than thyroglobulin. Lancet 1:648-652, 1959.
3. Burnet, F. M.: The new approach to immunology. New England J. Med. 264:24-34 (January 5) 1961.
4. ——: Auto-immune disease. I. Modern immunological concepts. II. Pathology of the immune response. Brit. M. J. 2:645-650; 720-725, 1959.
5. Paterson, P. Y.: Transfer of allergic encephalomyelitis in rats by means of lymph node cells. J. Exper. Med. 111:119-136 (January 1) 1960.
6. Algire, G. H., Weaver, J. M. and Prehn, R. T.: Growth of cells in vivo in diffusion chambers; survival of homografts in immunized mice. J. Nat. Cancer Inst. 15:493-507 (December) 1954.

# Early Recognition and Treatment of Hepatitis

WILLIAM D. DAVIS, JR.*

*Ochsner Clinic, New Orleans*

*Hepatitis in a general civilian hospital is accompanied by a high incidence of complications and a significant mortality.*

*Early diagnosis and prompt treatment will minimize the dangers of the disease, and meticulous attention to sterilization and isolation technics will prevent transmission within the hospital.*

*Careful evaluation of the necessity for blood transfusion and careful screening of blood donors will reduce the transmission of homologous serum jaundice.*

WILLIAM D. DAVIS, JR.

CONTRARY to the usual military and institutional experience, the occurrence of viral hepatitis in a general hospital and clinic practice represents a serious problem associated with a high incidence of prolonged morbidity and a significant mortality. The general opinion expressed in the medical literature is that viral hepatitis is attended by a mortality of less than 1 per cent and that it is rarely, if ever, followed by cirrhosis.

A review of our experience with 207 cases of viral hepatitis encountered at the Ochsner Foundation Hospital and Ochsner Clinic during the last 15 years contradicts these reports. One-third of our patients experienced prolonged morbidity or complications, and 10 per cent died. These figures were the same for ordinary infectious hepatitis as for homologous serum jaundice. Half of the patients who died had acute fulminant hepatitis with an extremely rapid course; one-third died as a result of postnecrotic cirrhosis, and one-fifth had cholangiolitic hepatitis. Surgical intervention contributed significantly to the mortality in the last-mentioned group because of the difficulty of differentiating this condition from extrahepatic obstructive jaundice. Abdominal exploration was necessary in some of these patients and contributed directly to death in three. Thirty-four patients in the entire group had postnecrotic cirrhosis. Seven of these patients died; 16 continued to have chronic hepatic disease, and only 11, or less than half, recovered. The patients with cholangiolitic hepatitis constituted only 7 per cent of the entire group, and one-third of them died. Three had chronic hepatic disease, and approximately one-half recovered completely.

The patients in this series were considerably older than commonly seen. The maximal number of cases occurred in patients in the

*Department of Gastroenterology, Ochsner Clinic, New Orleans, Louisiana.

Presented before the forty-fifth annual Assembly of the Interstate Postgraduate Medical Association at Pittsburgh.

fourth and fifth decades of life. The chief symptoms were malaise, jaundice, anorexia, nausea and abdominal pain; however, significant pruritus occurred in one-fifth of the patients, a sufficient incidence to detract considerably from its value in differentiating obstructive jaundice from acute infectious hepatitis. The physical signs were also those commonly reported: a large, tender liver, jaundice, fever, and an occasional enlarged spleen. A common valuable finding was a small, relatively soft lymph node situated at the level of the right seventh transverse cervical process in the posterior portion of the neck, known as the hepatitis node. Lymphadenopathy in other sites, including the left side of the neck, may be associated with hepatitis, and the frequency with which this node can be found is of diagnostic help.

In searching for an explanation for the relatively high mortality in this series, we found a surprising incidence of severe hepatitis after severe debilitating illnesses of other cause, particularly diseases that require transfusion of large amounts of blood. Typically, in these instances, the hepatitis was of brief duration and of a fulminant type, which was attributed to the patient's lowered resistance caused by other illness. Pregnancy also was found to be importantly associated with the more severe types of hepatitis. These patients, together with those with cholangiolitic hepatitis who were operated on, accounted for the greatest number of deaths.

### *Prevention*

In view of the rather serious nature of hepatitis in the type of patients described, the question of prevention is most important. Improvement in technics of sterilization within the hospitals is of benefit. The universal autoclaving of all sticking or cutting instruments greatly reduces cross infection from patient to patient within the hospital. Strict fecal isolation, with sterilization of bed linens and bedpans, careful hand washing, and meticulous care of the fingernails, also minimizes fecal-borne infection within the institution. This is particularly important in pediatric and chronic illness wards. The necessity for isolation beyond this has not been established.

Careful examination of the indication for blood transfusion and, of course, careful screening of blood donors will also minimize the possibility of homologous serum jaundice. Every blood transfusion entails a definite risk of transmission of hepatitis, and the benefit to be gained from replacement of blood must be carefully weighed against the possible risk. If serum proteins or plasma expanders are the needed replacement, serum albumin or pooled plasma, which has been stored for six months at room temperature, is much safer than whole blood.

In fecal-borne infectious hepatitis, gamma-globulin prophylaxis is extremely valuable. Recently, it has in many instances induced a passive-active type of resistance related to suppression of an already-incubating infection. A 10 cc. ampule of gamma-globulin is necessary to immunize most children for from six to eight weeks.

### *Symptoms*

Loss of appetite, loss of taste for cigarettes, an achy feeling, loss of energy, mild nausea, and slight discomfort in the upper part of the abdomen alert the clinician to suspect the possibility of hepatitis. Tenderness on fist percussion over the liver or on palpation of the liver, bilirubin in the urine, demonstration of a hepatitis node or a palpable spleen, and additional appropriate laboratory studies aid in establishing the diagnosis. Parenthetically, it should be noted, however, that a palpable spleen does not exclude a diagnosis of carcinoma of the pancreas, since approximately 15 per cent of patients with carcinoma of the pancreas will exhibit a palpable spleen secondary to splenic hypertension produced by invasion of the splenic vein.

A normal to low total leukocyte count, with a tendency toward granulocytopenia and lymphocytosis, and a normal sedimentation rate strongly favor a diagnosis of hepatitis rather than obstructive jaundice. BROMSULPHALEIN® retention of more than 50 per cent, with or without clinical jaundice, and extremely high levels of serum glutamic oxaloacetic and pyruvic transaminases, together with alkaline

phosphatase (which may be normal to moderately elevated), are the hallmarks of hepatitis. The flocculation and turbidity values are usually elevated. A significant number of patients with hepatitis are anicteric, so the presence of jaundice should not be demanded before hepatitis is suspected.

Microscopic examination of a specimen of the liver obtained by needle biopsy can be extremely valuable in differential diagnosis in cases of granulomatous lesions of the liver as well as in mechanical types of obstructive jaundice. It is well to bear in mind that the risk of biliary peritonitis, which results from puncture of a biliary radicle during performance of needle biopsy, is somewhat increased in the presence of mechanical biliary tract obstruction. In our experience this risk has been substantially less than that of surgical exploration of the abdomen, and the results in differential diagnosis have been almost uniformly good.

### *Treatment*

Treatment of early uncomplicated hepatitis consists chiefly of adequate bed rest and nutrition. A high-caloric, high-protein diet without restriction of fat is well tolerated by most patients and is the diet of choice. In the initial anorectic phase of the disease, the daily intravenous infusion of 1000 to 3000 cc. of a 10 per cent solution of glucose may be extremely helpful in early restoration of appetite. Complete bed rest, except for bathroom privileges, is the rule until the patient feels well and the bilirubin has been substantially reduced. Vitamins are of probable but questionable value at this stage of the disease; at the most, a modest supplement is indicated. Crude brewer's yeast powder (0.5 oz. three times a day) has seemed to us to be beneficial. It is best tolerated in tomato or grapefruit juice.

Full activity is gradually resumed after the patient feels perfectly well and the bilirubin has decreased below the level of 3 mg. per 100 ml. Periodic check of the bilirubin and Bromsulphalein retention as activity is resumed is wise. Significant reversal of the trend toward normality should indicate additional bed rest.

Corticosteroids are not indicated in the treatment of uncomplicated hepatitis, but have seemed to us to be of considerable value in both the acute fulminant type of hepatitis and the type which tends to remain chronically active beyond a period of approximately eight weeks. The most obvious effects of these agents are in increasing the appetite and well-being of the patient. There is almost always significant reduction in the serum bilirubin and Bromsulphalein retention, but not necessarily concomitant improvement in the microscopic picture of the liver. Once corticosteroids are given, it may be necessary to continue their use for a long time, as frequently, after withdrawal, there may be objective and subjective evidence of recurrence. The program usually followed entails use of an initial dosage of 40 mg. of prednisone daily, with quick reduction to 20 mg. daily, followed by more gradual reduction to approximately 5 mg. daily as the results of the liver function tests return to the base line. This dosage should be maintained for from weeks to months, until it can be gradually withdrawn without evidence of recrudescence.

Protein must be eliminated for a few days from the diet of the patient with hepatic precoma or coma. All nitrogenous materials must be removed from the intestine, if possible. This can be efficiently accomplished with small doses of magnesium sulfate repeated several times daily in addition to the use of saline flushes. Nonabsorbable antibiotics, such as neomycin or paramomycin, in a dosage of 1 to 2 gm. four times daily, are beneficial in reducing bacterial activity in the intestinal lumen. This is of particular importance if coma has resulted from large amounts of blood in the gastrointestinal tract. The need for supplementary potassium is determined by laboratory demonstration of deficiency, as in some instances hyperpotassemia may also be present. Systemic administration of antibiotics is probably of importance in controlling infection elsewhere and bacterial showers brought to the liver by the portal blood. Corticosteroids may be of help during this phase of acute hepatitis, but the evidence in favor of their use is controversial.

# Viral Diseases; Their Control by Immunologic Means

JONAS E. SALK*

*University of Pittsburgh School of Medicine, Pittsburgh*

*It has long been held that a killed-virus antigen would not induce complete immunity, that the effect would be transient, and that many injections would be required. These preconceptions are false. An adequate antigenic stimulus with killed-virus poliomyelitis vaccine will induce long-lasting and possibly permanent effects. It is also possible that durable immunity can be induced by a single antigenic stimulus if it is sufficiently potent.*

*Exciting possibilities for the future include the addition to the poliomyelitis vaccines of other viruses that may behave in the same manner, to permit induction of immunity to many diseases at the same time. Very little new knowledge is required for this to be possible, and technics for acquiring the knowledge are at hand.*

JONAS E. SALK

HAVE you ever thought of the possibility of life without viruses? I am sure that those who have gone before us have not, in their day-to-day thinking, thought of life without smallpox, bubonic plague, diphtheria, tuberculosis, venereal diseases, typhoid, the enteric diseases that are especially devastating in the early months of life, malaria, yellow fever, streptococcal diseases and their complications, pneumonia, typhus—and I could go on. Have you ever considered the unexpected benefits that have accompanied the elimination of many of these diseases?

Let me cite some of the medical problems, to say nothing of the personal and social problems, of persons who survived these infections and bore their effects, many of which at first were not known to be the consequences of the infections and only later were causally related to a recent or remote event. Consider the blemishes of smallpox, which led to development

*Virus Research Laboratory, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

Aided by a grant from The National Foundation.

Presented before the forty-fifth annual Assembly of the Interstate Postgraduate Medical Association at Pittsburgh.

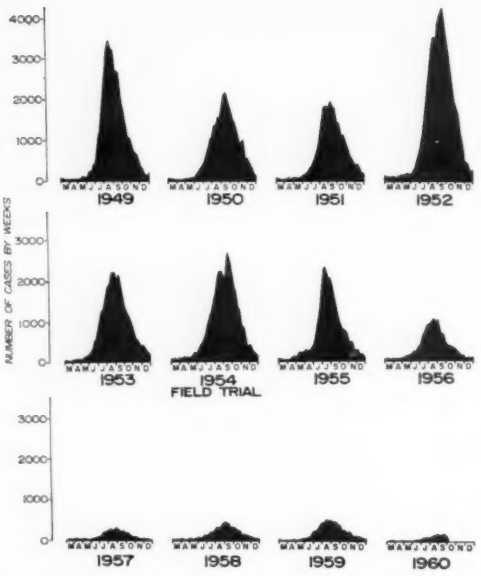



FIGURE 1. Incidence of poliomyelitis in the United States, March through December.

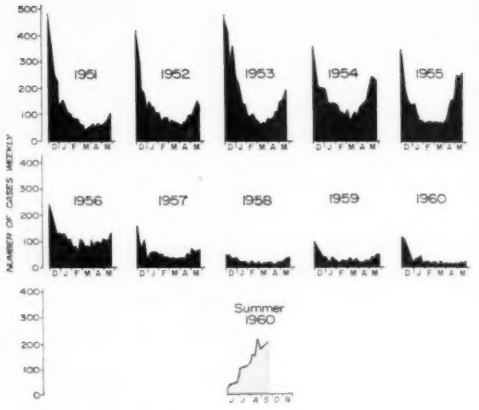



FIGURE 2. Incidence of poliomyelitis in the United States, winter and spring months.

(Figures 1 and 2 are from information obtained from the United States Public Health Service through The National Foundation.)

of the forerunner of adhesive tape (long called court plaster) to cover the scars. The complications of tuberculosis such as Pott's disease, tuberculosis of the urinary tract, tuberculous meningitis, and adrenal insufficiency are familiar to you. Diphtheritic myocarditis and adrenal disease due to the effects of diphtheria toxin, the neuropathies, syphilitic aneurysm of the aorta, and general paresis in its various forms are things of which we need not be reminded. Typhoid fever, the multicellular parasitic diseases, and the dysenteries, including the chronic effects of amebic infestation, have been reduced sharply in this country because of the environmental controls that have kept them from contributing the share they once did to the museum of medical mementos.

Side benefits have accrued from the use of antibiotics in treatment and control of the spread of streptococcal diseases. Reduction in the incidence of rheumatic fever (and consequently of subacute bacterial endocarditis), acute nephritis, infections of the middle ear, and mastoiditis has followed the development of methods for partial control, at least, of streptococcal disease.

For some time I have been interested not only in trying to understand some of the basic characteristics of viruses and of immunologic mechanisms as matters about which I have been curious, but also in the possible consequences of putting together relevant bits of knowledge that might bring about the control of diseases caused by viruses. I am now especially curious about the consequences that conceivably might follow such control. By and large I have been reluctant to speculate about these possibilities other than in the privacy of the places where I do my thinking and in the laboratory where experiments are designed and carried out. However, I may soon relax in this respect, because some of the speculations and imaginings of several years ago are beginning to come true, and possibly some of the things I now think about from time to time may come true in the future.

It would be idle folly to dream about a life without viruses, at least those viruses that are the cause of some of our obvious problems (and perhaps those that are not the obvious cause of other equally important problems whose cause is still not clear), unless we had at our disposal a means to control the viral diseases, to eliminate them from our environment as we were able to do with typhoid and dysentery. The problem before us is the con-

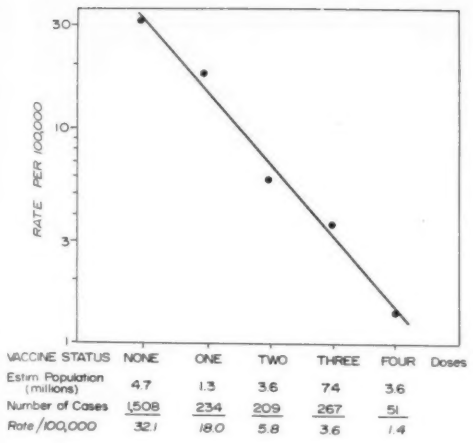

RATE PER 100,000
30
10
3
1
VACCINE STATUS NONE ONE TWO THREE FOUR Doses
Estim Population (millions) 4.7 1.3 3.6 7.4 3.6
Number of Cases 1508 234 209 267 51
Rate/100,000 32.1 18.0 5.8 3.6 1.4

FIGURE 3. Rates of paralytic poliomyelitis in 1959 among children four years old and younger according to vaccination status. Straight line describing reduction corresponding to number of doses of vaccine has important implications (see text).

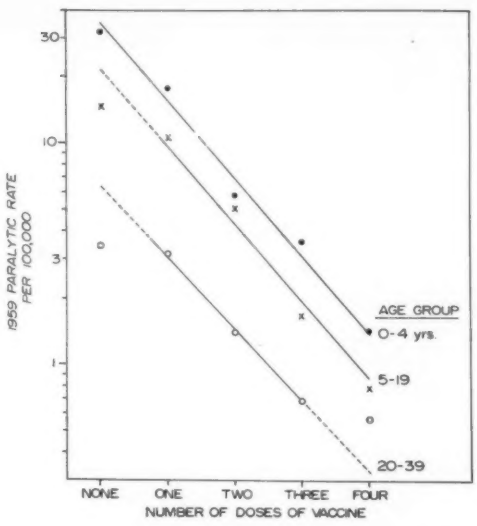



FIGURE 4. Rates of paralytic poliomyelitis in 1959 among various age groups according to vaccination status. Parallelism of lines suggests corresponding degrees of efficacy of vaccination at all age levels.

trol of viruses at whatever point they may be vulnerable in the course of transmission. In the absence of chemical and physical means, one way of so doing seems to be the use of immunologic methods. I could illustrate this idea in a number of ways, but I will use poliomyelitis as an example since this disease continues to be of practical interest to you and because it is likely that the principles involved will, in time, prove applicable to a wide variety of viral diseases—with the consequence, I believe, that man will some day be the master and viruses can be controlled. I will leave, however, to others or to another time a discussion of the will to do when the means exists.

I will begin by reviewing the effects of the use of poliomyelitis vaccine in the United States in the past six years. Figure 1 illustrates the incidence of poliomyelitis in the United States from 1949 to the middle of October 1960. The vertical scale indicates the number of cases per week from March to December. The mountainlike peaks reflect the seasonal rise in weekly incidence in the years before the field trial, and I call your attention to the fact that in any given week at the height of the season there were between 2000 and 4000 cases. Vaccine was introduced in 1954, and the pattern that evolved thereafter is clear. By the middle of October 1960 the total cases for the year numbered about 2500, with an estimate for the entire year being perhaps slightly more than 3000. This is noteworthy when one considers that in any one of a number of successive *weeks* in the years 1949 and 1952 the score was of this magnitude.

To illustrate the pattern of the disease, not merely during the summer and fall but in the winter and spring as well, figure 2 presents the incidence of poliomyelitis from December through May in the years from 1951 to 1960. I call your attention to the reduced incidence in what might be called the interepidemic period. For comparison, the incidence of poliomyelitis in the summer of 1960 is shown, and you will observe that even in August and September 1960 there was less disease than there was in December and January of the prevaccination years.

Are these effects due to vaccination or do they merely represent normal fluctuations in incidence of the disease? Figure 3 plots the 1959 paralytic rate in the age group of zero to four years against the number of doses of

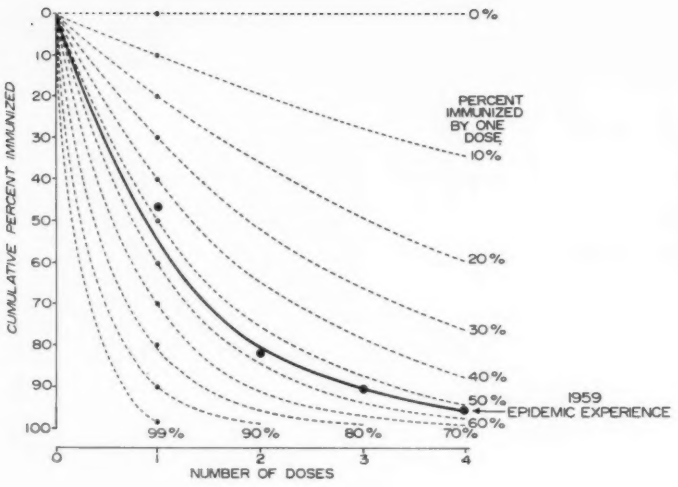



FIGURE 5. Cumulative percentages of immunity after multiple injections of vaccines of different hypothetical potencies. Line plotted from 1959 epidemic experience follows theoretical calculation reasonably closely.

vaccine, on a logarithmic scale. The rate is calculated from the estimated number of children in this age group who did not receive vaccine. In 1959, there were 4.7 million children aged four years or less who had not received vaccine, and in this group there were 1,508 cases of paralytic poliomyelitis, or 32.1 per hundred thousand. The rate decreased according to the number of doses of vaccine, ranging from 18.0 per hundred thousand for 1.3 million children who had received one dose to 1.4 per hundred thousand for 3.6 million children who had received four doses of vaccine.

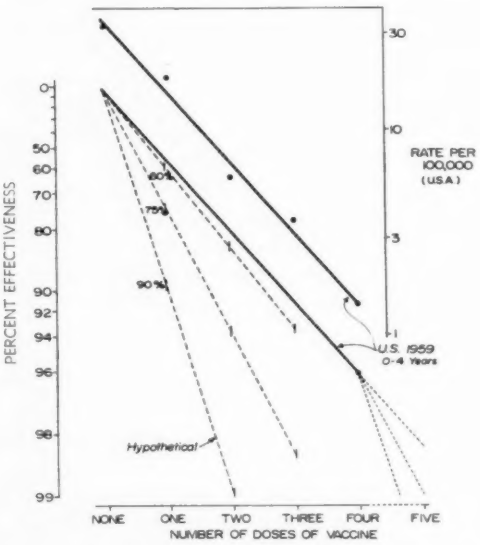



FIGURE 6. Hypothetical comparison of observations depicted in figure 3 with vaccines of different potencies. A line drawn parallel to the line shown in figure 3 and put on a percentage scale indicates that four doses of vaccine have reduced the probability of paralysis by about 96, and three doses by about 90 to 92.

The unexpected finding was the way these points fell in a straight line. This was rather surprising and presented rather important theoretical as well as practical implications. Anticipating what I will say in a moment, the point indicating the rate of paralytic poliomyelitis among children who had received four doses of vaccine is 96 per cent lower than the point indicating the rate among unvaccinated children, which would mean 96 per cent effectiveness or a 96 per cent reduction in probability of paralysis.

The downward slope of the line depicting paralytic rate in the age group of zero to four years was also observed for the age groups from 5 to 19 and from 20 to 39 years (figure 4). These data have been discussed fully in a paper published in the October 1, 1960 issue of the *Lancet*. I merely want to call attention to the parallelism of the lines, suggesting corresponding degrees of efficacy of vaccination at all age levels. It was to be expected that the lines would be lower as the age scale

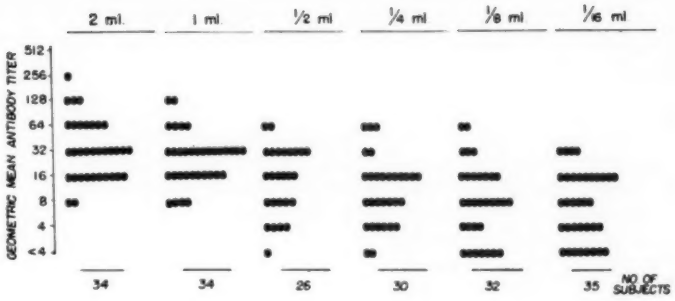



FIGURE 7. Type 1 antibody response two weeks after intramuscular administration of one dose of Reference Vaccine A to subjects without demonstrable preantibody to any type. Degree of response is related to potency of vaccine.

(From Salk, J. E.: Considerations in the preparation and use of poliomyelitis virus vaccine. J.A.M.A. 158:1239, 1955.)

advanced, because of the naturally acquired immunity.

The straight line means that if a single dose of vaccine immunized a certain percentage of all susceptible persons, a second dose would immunize the same proportion of the remaining susceptible persons, a third dose would immunize the same proportion of those remaining, and so forth. It is a typical line such as describes the half-life or decay of a radioactive substance, for example.

The observations described by these straight lines have a rather important practical bearing and take on more meaning when one examines figure 5. The vertical scale indicates the cumulative percentage immunized after multiple injections of vaccines of different hypothetical potencies, and the horizontal scale the number of doses of vaccine. The postulate is that if a vaccine is totally ineffective after one dose, it will be ineffective after two, three or four doses; if it is effective in 10 per cent of persons after one dose, a second dose will immunize an additional 10 per cent, and so forth, describing a line that would slope as indicated. If a vaccine were 30 per cent effective after one dose, it would immunize up to 75 per cent by the fourth dose. It follows that it would be possible for vaccine to be 99 per cent effective after one dose, and theoretically to approximate 100 per cent effectiveness after one dose. This hypothetical speculation was tested by the 1959 epidemic experience, and you can see that when the points were plotted the observed line followed the theoretical one reasonably closely. This means that we now understand enough about the mechanisms of action of an immunizing agent of this kind to be able to predict rather closely the effects with one dose or more than one dose. More importantly, it allows the theoretical speculation, which I think is not unrealistic, that it should be possible to immunize with a single dose of vaccine.

Figure 6 illustrates the same point another way. Much of this analysis was carried out in order to answer the question, How many doses of vaccine are necessary to achieve full protection? Vaccines of different hypothetical potencies are compared with the observed effectiveness of one or more doses of vaccine in 1959 in the age group of zero to four years (plotted in figure 3). A line drawn parallel to the one shown in figure 3 and put on a percentage scale indicates that four doses have reduced the probability of paralysis by about 96 per cent, and three doses have reduced it by about 90 to 92 per cent. If a vaccine were 60 per cent effective after the first dose, or 75 or 90 per cent effective, higher percentages of effectiveness would be achieved with fewer doses. One can also see that administration of a fifth dose, using vaccine of the same order of potency as that which has been available, would increase the protection along the same line; if the vaccine were 75 or 90 per cent effective, the increase in protection rate would descend more abruptly.

The purpose in presenting these data is to indicate that we now have a mathematical understanding of the meaning of effectiveness in relation to number of doses of vaccine and to potency of the vaccine.

How practical and realistic is it to expect that immunization against poliomyelitis, and perhaps against other viral diseases, might be

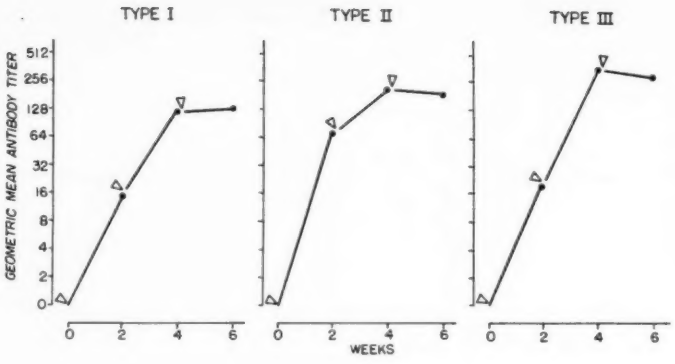



FIGURE 8. Geometric mean titer of antibody after each of three doses of Reference Vaccine A, 1 ml. intramuscularly, at two week intervals, in 20 subjects without preantibody to any type.

(From Salk, J. E.: Vaccination against paralytic poliomyelitis: Performance and prospects. Am. J. Pub. Health 45:575, 1955.)

effective after a single dose? In figure 7, each dot represents one person. The number of subjects in the various groups ranges from 26 to 35. A single dose of a Reference Vaccine was given to these subjects in a titration series beginning with 2 ml. and decreasing to 1/16 ml. The vertical scale indicates the geometric mean antibody titer two weeks later. You can see that potent material can induce antibody formation in all persons. When the material is less potent, the degree of effectiveness is somewhat less, in the sense that more persons do not respond.

It was first suggested that three doses of vaccine should be given in a sequence wherein two doses were followed by a third seven months later. Figure 8 shows the antibody response to three doses of vaccine given at two week intervals. After the third dose, the antibody level did not rise as it did after the first two doses, and consequently it was suggested that the third dose be postponed. Figure 9 indicates that when the third dose was postponed until a year after the second dose, the antibody response was very high. You are all familiar with the booster phenomenon and will recognize that it is important in raising antibody titer to high levels. The point I wish to make is that we now believe it is unnecessary to have such high levels of antibody for immunity to poliomyelitis. You will discover the meaning of this statement in a moment.

Figure 10, showing the antibody response after a booster dose in relation to the potency of vaccine used for primary inoculation and in comparison with the antibody titer follow-

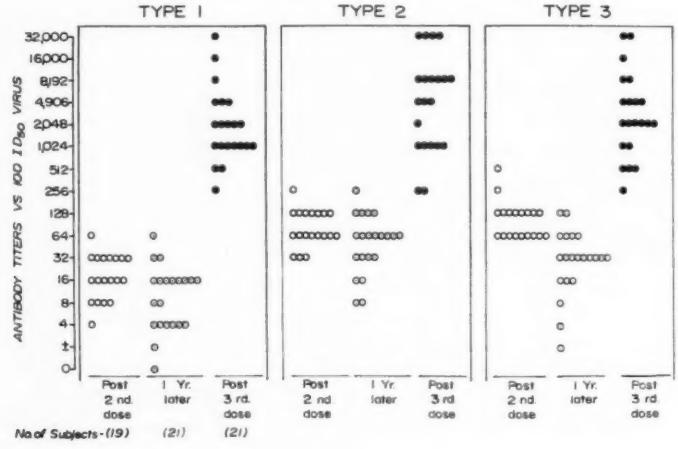



FIGURE 9. Persistence of primary response and degree of booster response to two 1 ml. doses of Reference Vaccine A given two weeks apart and 1 ml. Vaccine J given one year later to children without antibody to any type before their vaccination.

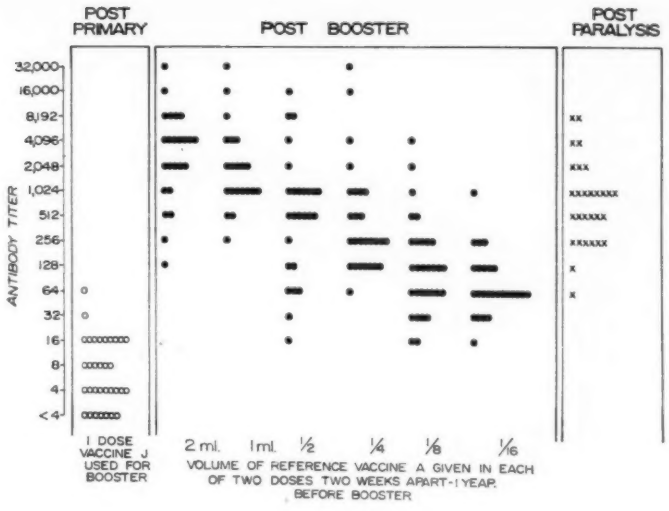



FIGURE 10. Type 1 antibody response after booster in relation to potency of vaccine used for primary inoculation and in comparison with antibody titer following natural infection.

(Figures 9 and 10 are from Salk, J. E.: Antigenic potency of poliomyelitis vaccine; influence on degree and duration of vaccine effect. J.A.M.A. 162:1451, 1956.)

ing natural infection, demonstrates that the response to a booster dose is influenced by the intensity of the first antigenic stimulus. The subjects depicted are the ones whose initial response to different quantities of antigen is shown in figure 7. A year later, each was given a constant booster dose. The booster phenomenon is not an all-or-none effect, but is one whose intensity is influenced by the intensity of the first dose of vaccine. Comparison of the antibody response of the vaccinated subjects with the levels of antibody following paralysis (right-hand frame of figure 10) reveals that it is possible, with a killed-virus vaccine, to induce antibody levels greater than those induced even by a natural infection; but one can also induce a lesser response, depending on the potency of the antigen.

One, two and three years after administration of the booster dose, the high antibody levels persisted in the subjects who had received potent doses initially (figure 11). Antibody levels were somewhat lower for the subjects whose first doses of vaccine were less potent. These observations are intended to indicate the tendency for antibodies to persist at whatever level is present at the one year postvaccination point; and it may be low or high, again indicating the importance of potency of vaccine used for the initial dose.

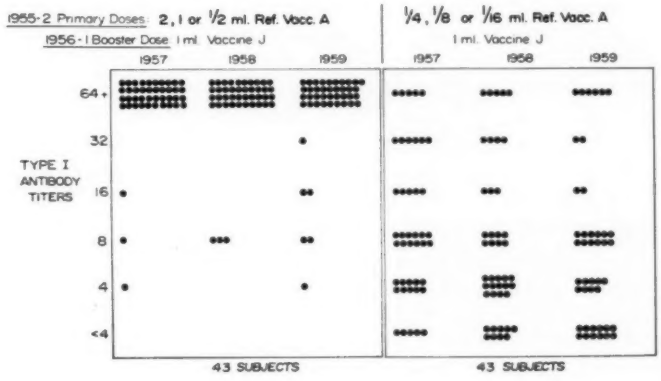



FIGURE 11. Persistence of high antibody titers up to three years after booster dose in relation to potency of vaccine which was used for primary immunization.

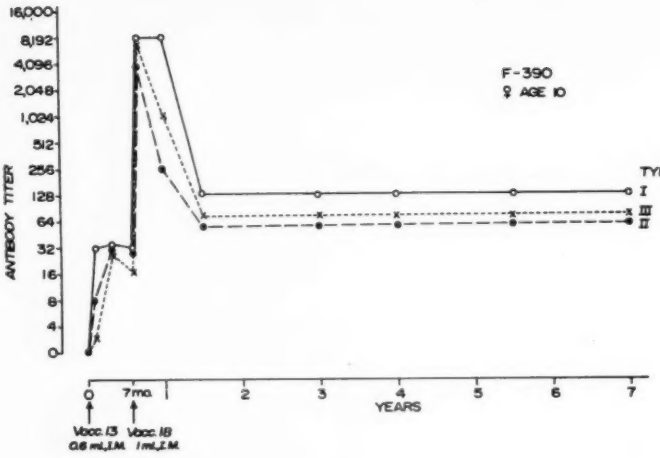



FIGURE 12. Antibody titers of 10 year old child followed for seven years. Response is typical of that seen in many children and is not an isolated finding (see figure 13).

Figure 12 is a chart depicting the antibody response of a child, 10 years old initially, whom we have followed for seven years. It typifies observations in other children whom we have followed for this length of time. A primary response followed the initial dose of vaccine, and the booster effect was observed at seven months. A seemingly sharp decline ensued over a period of a year, and there has been a plateau for approximately six years after the booster dose. This bears on the question that interests all of us, namely, How long does immunity last after the use of a killed-virus poliomyelitis vaccine, and is it necessary to give repeated annual injections to sustain immunity? I think the chart in figure 12 should answer the question in part. Figure 13 represents observations in 13 children and shows the course of the antibody levels for six years following administration of the booster dose. The titers of type 3 antibody are depicted here, but the same course is evident for types 1 and 2. The persistence shown in figure 12 is not an isolated observation.

Figure 14 is intended to show that persistence of antibody levels is evident after primary immunization even when a booster dose is not given. The seven year old child whose chart is reproduced received three doses of field-trial vaccine two weeks apart. We regard this as primary immunization because of the relatively short interval between doses. You can see the degree of persistence of antibodies. In other instances we have observed seven

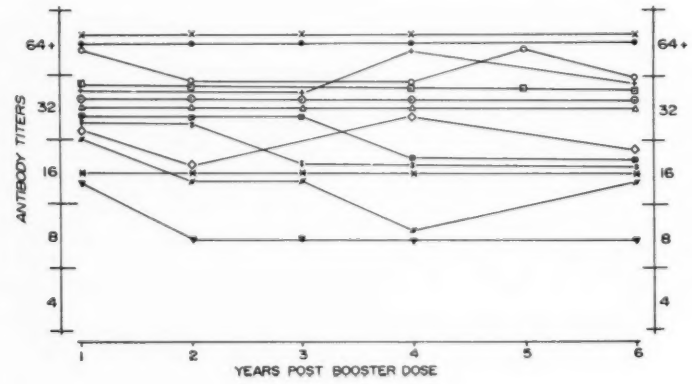



FIGURE 13. Type 3 antibody levels one to six years following booster dose in 13 triple-negative children (two doses two weeks apart, third dose seven months to one year later).

(Figures 3 through 6 and 11 through 13 are from Salk, J. E.: Persistence of immunity after administration of formalin-treated poliovirus vaccine. Lancet 2:715, 1960.)

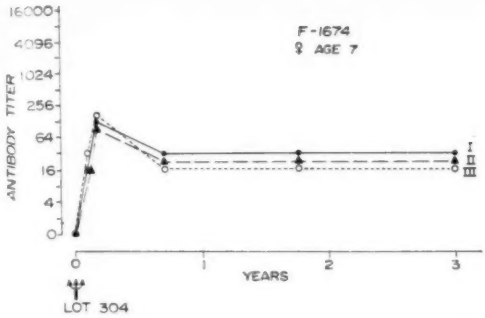



FIGURE 14. Persistence of antibody three years after primary vaccination. Booster dose was not given.

(From Salk, J. E.: Preconceptions about vaccination against paralytic poliomyelitis. Ann. Int. Med. 50:813, 1959.)

year persistence after primary immunization. These were all rather surprising observations. Dr. Gordon Brown of the University of Michigan has also observed this persistence.

Figure 15 reproduces the line describing the relationship between number of doses of vaccine and its effectiveness in 1959 for the age group of zero to four years and presents a line describing this relationship for 1960 (through September 19). The relationship is essentially the same for the two years.

I can summarize all that I have tried to indicate up to now by saying that it appears that if vaccine is of sufficient potency one should be able to immunize with a single dose, and consequently the goal will be to produce antigens of that degree of potency. But I now want to emphasize the fact that this is not the limiting factor in furthering the elimination of paralytic poliomyelitis in this country. The important and crucial factor is the extent of use of vaccine.

Figure 16 depicts a typical story that has recurred throughout the United States in the past several years. It shows the incidence of poliomyelitis among white persons and among nonwhite persons in Detroit in 1958. Poliomyelitis occurred in epidemic form among the Negroes but not among the white population. The reason was clearly a difference in degree of use of vaccine. This pattern has been observed in Des Moines, Iowa, in Providence, Rhode Island, in Little Rock, Arkansas, in

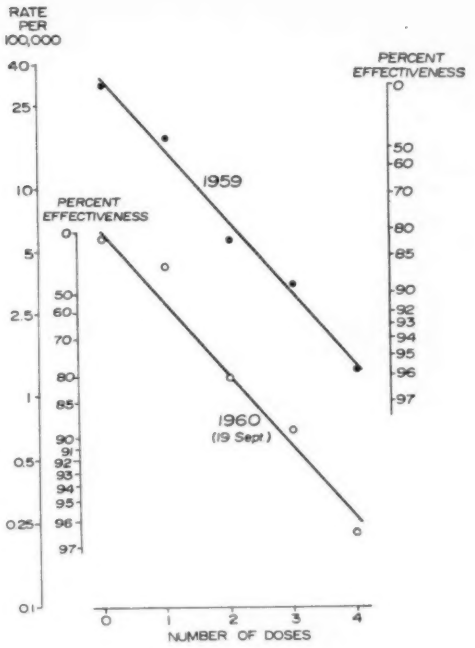



FIGURE 15. Rates of paralytic poliomyelitis, 1959 and 1960 (up to September 19), zero to four year age group, according to vaccination status.

Chicago and elsewhere throughout the country for the past several years wherever small outbreaks of poliomyelitis have occurred.

Figure 17 shows the estimated percentages of persons in the different age groups who had received three or more doses of poliomyelitis vaccine by April 1960. About 42 per cent of children less than five years of age had not had three doses; it is in this segment of the population that the disease has been occurring predominantly. In spite of the fact that a large segment of the population has not been vaccinated, it is interesting to note the striking effects of use of the vaccine (see figure 1).

The number of cases of paralytic and nonparalytic poliomyelitis per year since 1950 in Australia, Denmark and Sweden are tabulated in figure 18. These figures were obtained from World Health Organization reports. Combined, they reveal an average of about 6000 cases per year from 1950 to 1954 in a population of 21.9 million, or a case rate of 26.7 per

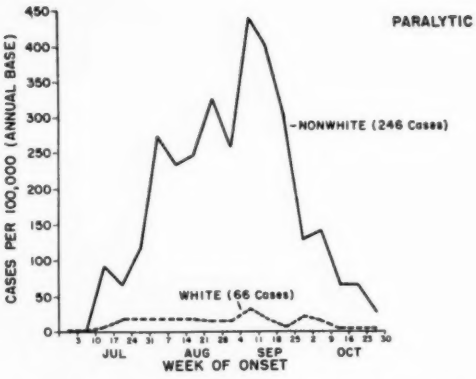



FIGURE 16. Attack rates of poliomyelitis, Detroit, 1958. Population estimates: white, 1,480,000; nonwhite, 420,000; total, 1,900,000.

(From Salk, J. E.: Vaccination against poliomyelitis: An ounce of prevention. Roy. Soc. Health J. 79:310, 1959.)

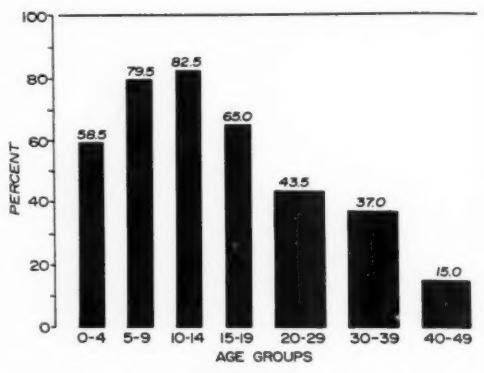



FIGURE 17. Estimated percentages of persons who had received three or more doses of poliomyelitis vaccine by April 1960.

(From projections prepared by The National Foundation, based on unpublished data of the National Office of Vital Statistics from population surveys conducted by the Bureau of the Census.)

hundred thousand. In 1959 the rate dropped by 97.5 per cent, and at the time the figures for 1960 were compiled (October 1) it had dropped by 99.5 per cent, with merely two cases in Denmark and seven in Sweden. It would appear that the experience has been somewhat better in these countries than it has been in the United States. The reason, I believe, is not principally any superiority in the vaccine available but rather that persons in the younger age groups have been systematically vaccinated. It is also true that these countries have smaller populations and geographical areas—but the data are highly suggestive.

All the cases of paralytic poliomyelitis in the United States in 1959 are charted in figure 19 according to age groups. Forty-three per cent occurred in children less than five years of age. Young mothers and fathers in the 20 to 29 year group were more affected than other young adults. The black portions of the columns indicate the percentages of cases among persons receiving fewer than three doses of vaccine. It would appear, therefore, that the black portions reflect failure to use vaccine, and the white portions the so-called vaccine failures at the three dose level.

The fluctuations in the incidence of poliomyelitis in the United States in the six years

| | Australia | Denmark | Sweden | COMBINED |
|---|---|---|---|---|
| POPULATION-millions | 10 | 4.5 | 7.4 | 21.9 |
| 1950 | 2267 | 1572 | 1718 | 5557 |
| 1951 | 4736 | 383 | 551 | 5670 |
| 1952 | 1743 | 5676 | 492 | 7911 |
| 1953 | 1677 | 1591 | 5090 | 8358 |
| 1954 | 1906 | 352 | 1009 | 3267 |
| 1955 | 874 | 70 | 486 | 1430 |
| 1956 | 1274 | 191 | 551 | 2016 |
| 1957 | 141 | 21 | 250 | 412 |
| 1958 | 110 | 66 | 191 | 367 |
| 1959 | 75 | 26 | 56 | 157 |
| 1960 | (26) | (2) | (7) | (35) |
| CASES | | | | 6152 |
| RATE/100,000 | | | | 26.7 |
| RATIO | | | | 100 |

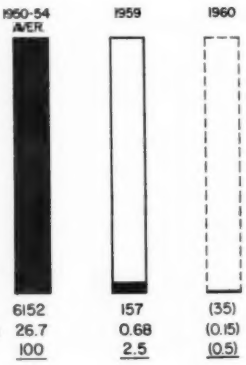



FIGURE 18. Incidence of poliomyelitis per year since 1950 in Australia, Denmark and Sweden.

(From data obtained from reports of the World Health Organization through Mr. Gabriel Stickle, The National Foundation.)

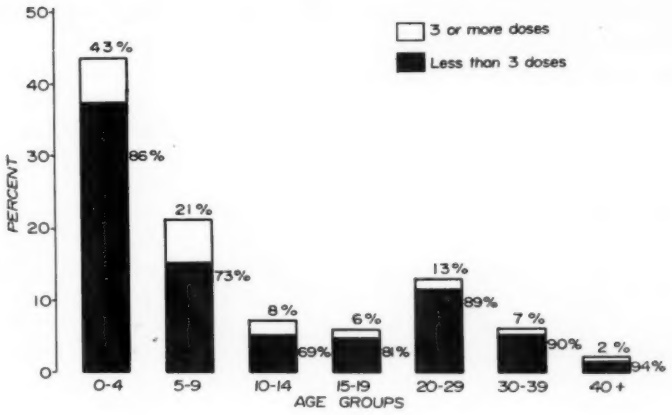



FIGURE 19. Percentages of cases of paralytic poliomyelitis in the United States in 1959 according to age groups and vaccination status.

(Figures 15 and 19 are from data obtained from the United States Public Health Service Poliomyelitis Surveillance Unit.)

before and the six years after the 1954 field trials are seen in figure 20. The consistent drop from an average rate of about 30 in the first six years to an estimated rate of about 1.5 cases per hundred thousand for 1960 is evident. How do we know this rate is not going to go up again, and how does this look in the longer perspective? Figure 21 shows, on a logarithmic scale, the fluctuations in incidence of poliomyelitis in the United States since 1915. There was a low incidence in 1938 and there was a rather high incidence in 1916. The logarithmic decline can descend far below the point estimated for 1960; the Scandinavian countries and Australia are near the bottom of the chart, and we will be there soon.

### *Conclusion*

It does seem possible to control a viral disease with a so-called killed-virus vaccine. Why

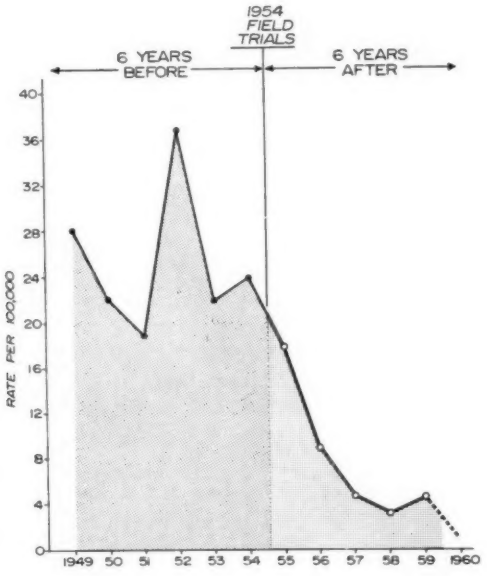



FIGURE 20. Annual incidence of poliomyelitis (rate per hundred thousand population) in the United States for the six years before and six years after introduction of vaccine.

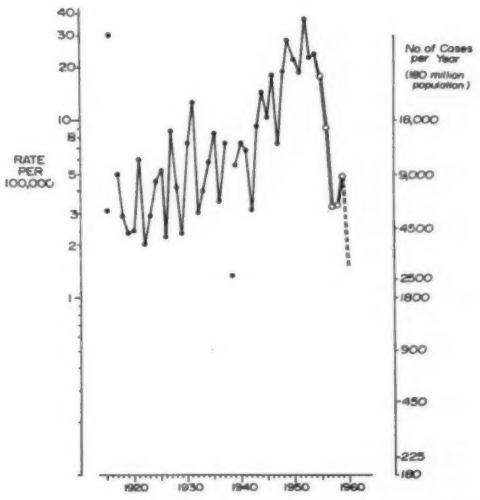



FIGURE 21. Fluctuations in incidence of poliomyelitis in the United States since 1915.

is this point important? Why does it matter whether a live virus or a killed virus is used? In part the question is of academic interest in the kind of discussion which goes on in scientific circles and which no one else cares about. The question is important in scientific circles because the idea has long prevailed that immunity induced by a killed-virus antigen would be incomplete, the effect would be transient, and many repeated injections would be required. It has also been said that only a live-virus vaccine can ultimately eradicate poliomyelitis; I prefer a less extreme word that would convey the idea of approximating extinction.

It is evident from the foregoing observations that these preconceptions were false, and we need not argue academically about whether persistence of antibodies is due to continued presence of live virus in the host or to repeated reinfections. It is clear that the facts require neither explanation, because an adequate antigenic stimulus with killed-virus poliomyelitis antigen will induce long-lasting and possibly permanent effects. In this respect academic discussion is of practical importance.

Other observations that are of both academic and practical interest are related to the possibility that durable immunity can be induced by a single antigenic stimulus if that stimulus is sufficiently potent. This is seemingly a new idea, but one that should have been entertained all along. Be that as it may, the exciting possibilities for the future include the addition to the poliomyelitis vaccines of other viruses which may behave in the same manner, to permit the induction of immunity to many diseases at the same time. Very little new knowledge is required for this to be possible, and technics for acquiring such knowledge are at hand. The more exciting idea is what life will be like without viruses.

## Books Received

**Books received are acknowledged by listing. As space permits, selected books are reviewed more extensively. Reviews in this issue start on page A-103; additional listings appear on page 170.**

**Surgical Diseases of the Lung.** By Buford H. Burch, M.D., Instructor, and Arthur C. Miller, M.D., Assistant Professor, Division of Surgery, College of Medical Evangelists, Loma Linda-Los Angeles. 128 pages, illustrated. 1961, Charles C Thomas, Springfield, Illinois. $8.50.

**Recent Advances in Renal Disease.** Proceedings of a conference at the Royal College of Physicians of London. Edited by M. D. Milne, Postgraduate Medical School, London. 254 pages, illustrated. 1961, J. B. Lippincott Company, Philadelphia and Montreal. $5.00.

**Atlas of Anatomy and Surgical Approaches in Orthopaedic Surgery—Lower Extremity.** By Rodolfo Cosentino, M.D., Research Associate, Department of Orthopaedic Surgery, State University of Iowa College of Medicine, Iowa City. Vol. 2. 264 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $14.00.

**Surgical Urology.** A handbook of operative surgery. By R. H. Flocks, M.D., Professor and Head, and David Culp, M.D., Associate Professor, Department of Urology, State University of Iowa College of Medicine, Iowa City. Ed. 2. 441 pages, illustrated. 1961, Year Book Medical Publishers, Inc., Chicago. $10.50.

**Systemic Lupus Erythematosus.** By Daniel L. Larson, M.D., Assistant Professor of Medicine, Columbia University College of Physicians and Surgeons, New York. 212 pages. 1961, Little, Brown & Company, Boston. $7.50.

**Management of Fractures, Dislocations and Sprains.** By H. Earle Conwell, M.D., Associate Professor of Orthopedic Surgery, Medical College of Alabama, Birmingham, and Fred C. Reynolds, M.D., Professor of Orthopedic Surgery, Washington University School of Medicine, St. Louis. Ed. 7. 1,153 pages with 1,227 illustrations. 1961, The C. V. Mosby Company, St. Louis. $27.00.

**Advances in Blood Grouping.** By Alexander S. Wiener, M.D., Senior Bacteriologist (Serology), Office of the Chief Medical Examiner, New York. 549 pages, illustrated. 1961, Grune & Stratton, Inc., New York and London. $11.00.

**Essential Pathology.** By Roger D. Baker, M.D., Professor of Pathology, Duke University School of Medicine, Durham. 638 pages with 470 illustrations. 1961, The Williams & Wilkins Company, Baltimore. $9.50.

**Rehabilitation and World Peace.** Proceedings of the Eighth World Congress of the International Society for the Welfare of Cripples. Edited by Eugene J. Taylor. 433 pages. 1960, International Society for Rehabilitation of the Disabled, New York. $2.00.

# A Biochemical Concept of Mental Disease

WILLIAM M. McISAAC*

*The Cleveland Clinic Foundation and*
*The Frank E. Bunts Educational Institute, Cleveland*

*Evidence strongly favors an abnormal serotonin metabolism as an etiologic factor in some forms of mental disease, and it is possible that under certain circumstances a harmala alkaloid, endogenously produced, could cause a psychotic state; such a state would tend to be chronic because of a chemical feedback mechanism. Although only a theory, this hypothesis provides the fascinating motivation to fulfill Thudichum's dictate to study the normal brain chemistry "to its uttermost detail" so that eventually we may be able to isolate the "poisons fermented within the body" which are responsible for insanity.*

WILLIAM M. MC ISAAC

SOME 200 years ago the eminent chemist Boerhaave expressed the opinion that "the mind is in no way the subject of chemical investigation." It is surprising that this concept should have been accepted tacitly for so long, especially since mankind's knowledge of the effects of chemical compounds on mental processes dates back to prehistoric times, as evidenced by the finding of poppy heads in the kitchen middens of the Swiss lake dwellers.

Since time immemorial, primitive tribes all over the world have been making and taking plant extracts, in association with their ceremonies and rituals, in order to cause psychotic states and hallucinations. In South America, for example, the jungle vine *Banisteria caapi* has been used by Peruvian and Colombian Indians as a source of *caapi*, a potion which causes exhilaration followed by terror. Those who have taken *caapi* report seeing fantastic colorful visions followed later by terrifying hallucinations. Natives participating in the ceremony of *Yurupari*, driven to a frenzy by these delusions, savagely attack each other with whips.[1] The active principle in *caapi* has been extracted and identified as the alkaloid

*Research Division, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

Presented before the forty-fifth annual Assembly of the Interstate Postgraduate Medical Association at Pittsburgh.

harmine, and the pure alkaloid also has been found to produce hallucinations in man under experimental conditions.

The effects of drugs on the thought process seem to have been of particular interest to novelists through the ages. Among the writers who have described these effects from personal experience are such distinguished men as De Quincey, Baudelaire, Dumas and Aldous Huxley.

This should have been evidence enough that if abnormal mentation could be produced by chemical compounds, a chemical cause for organic mental disease should be sought. In fact, as long ago as 1884, Thudichum,[2] the pioneer of brain chemistry, wrote: "Many forms of insanity are unquestionably the external manifestations of the effects upon the brain substance of poisons fermented within the body. These poisons we shall, I have no doubt, be able to isolate after we know the normal chemistry to its uttermost detail. And then will come in their turn the crowning discoveries to which our efforts must ultimately be directed, namely, the discoveries of the antidotes to the poisons and to the fermenting causes and processes which produce them."

The time, however, was not ripe, and this prophetic statement fell on deaf ears. Little or no progress was made along these lines until very recently. Only during the past two decades have salient discoveries been made of a magnitude sufficient to give the required impetus to this field of investigation, and it is well worthwhile to reconsider some of these.

A scientific accident, as usual, was the first step. In 1943, Dr. A. Hofmann of the Sandoz Laboratories in Switzerland became ill while at work synthesizing derivatives of the ergot alkaloids. It was difficult for him even to reach home because of "fantastic pictures of extraordinary plasticity and intensive color surging towards him." The illness was transient and Hofmann concluded that he must have ingested a minute amount of the compound he had been making, lysergic acid diethylamide (LSD), and that this was the cause of his trouble. He proved this easily enough by deliberately taking LSD and making himself violently ill.

Later it was found that as little as 0.1 mg. of LSD could produce a psychotic state in a normal subject for several hours. In many ways these experimentally produced psychotic episodes are indistinguishable from schizophrenia. One example of this similarity is found in the following illustration. When Hofmann first discovered the hallucinogenic properties of LSD he got an artist to draw a portrait of him. Then the artist was given a small dose of LSD, and while under its influence he drew portraits at various time intervals. The elaboration of the drawings as the intoxication increased was noticeable, and at the height of the psychotic effect the artist's impression of what he saw consisted of surrealistic confusion of vivid colors. It is interesting to compare these pictures with a series drawn by a schizophrenic artist at different stages of his illness. The British artist Louis Wain, an eccentric bachelor who drew portraits of cats, provided such a series. Over a period of years he lapsed into a schizophrenic breakdown and his pictures of cats became less and less realistic until finally they were just fantastically elaborate designs.

I do not intend to suggest that surrealism and schizophrenia are synonymous. My intention is merely to underline the parallelism between the artist's impression of reality while under the influence of either a powerful psychotomimetic drug or a naturally occurring mental disease.

A truly major advance was made when the hormone serotonin was isolated by Rapport, Green and Page[3] at the Cleveland Clinic in 1948. In the ensuing 10 years, so many investigations centered around this compound that in a comprehensive review in 1958 Page[4] referred to some 682 papers concerning it.

Among the many pertinent discoveries, a few which stand out were the finding of serotonin in the brain,[5] the observation that the level of this hormone was related to reserpine tranquilization,[6] and the finding that LSD could antagonize its peripheral actions. These discoveries led Woolley and Shaw[7] of the Rockefeller Institute to conclude that "the naturally occurring mental disorders . . . for example schizophrenia . . . which are mim-

icked by these (psychotomimetic) drugs, may be pictured as being the result of a cerebral serotonin deficiency arising from a metabolic failure." And in Edinburgh Professor J. H. Gaddum[8] expressed the opinion "it is possible that the serotonin in our brains plays an essential part in keeping us sane."

So, by 1954, not only was the possibility that there might be a chemical basis for mental disease accepted but a particular compound had been incriminated. It is only fair to point out that there are many other theories concerning other compounds, and these have been reviewed by Kety.[9] Also, we should not make the elementary mistake of thinking that there may be only one cause for, say, schizophrenia, which probably is a blanket term for a multiplicity of mental aberrations.

The evidence incriminating serotonin appeared to be particularly strong, and it was very tempting to imagine what an abnormal serotonin metabolism could do, in view of the well-established example afforded by phenylpyruvic oligophrenia, a disease in which the abnormal metabolism of the amino acid phenylalanine results in subnormal intelligence. Incidentally, it has been shown recently that the abnormal metabolism of phenylalanine is the primary defect but that the toxic phenylpyruvic acid formed interferes with normal serotonin metabolism, causing a secondary defect.

Thus it seemed provident to explore the pattern of serotonin metabolism. It had been demonstrated that the major breakdown product of serotonin, due to the action of monoamine oxidase, was 5-hydroxyindoleacetic acid,[10] and measurement of this metabolite has proved to be of great value in the diagnosis of malignant carcinoid. This, however, was not the whole story. Erspamer[11] had found that excreted 5-hydroxyindoleacetic acid accounted for only about half of an administered dose of serotonin. This posed the problem of what happened to the rest of it. To solve this problem, we administered radioactive serotonin to animals and studied the urine chromatographically. At least five metabolites were present, one of which proved to be N-acetylserotonin.[12] These metabolites, however, appeared to be physiologically inactive, and only later was the significance of the production of acetylserotonin realized.

### *Structure-Action Relationship of Psychotomimetic Compounds*

There are two lines of approach to a better understanding of mental disease: (1) elucidation of the normal chemistry of the brain and (2) study of those compounds which can cause a psychotic state. Study of the relationship between chemical structure and psychotomimetic activity is likely to be a very rewarding approach but fraught with difficulty. The major problem is to discover a satisfactory procedure for assay. If one is interested in hypertension, it is relatively easy and quite objective to measure the effects of drugs on blood pressure. This is not the case with compounds possessing psychotomimetic activity, because the experience elicited in man is largely subjective and because it is doubtful what interpretation we should place on results in lower animals, which are not credited with any great powers of thought. Nevertheless, some objective comparison of relative psychotomimetic activity was necessary, so we have used a method in which rats are trained to escape from an electric shock by going from one side of a divided cage to the other when they see a warning light. The compound to be investigated is administered to rats so trained, and their performance is assessed by the number of times they fail to respond in the correct conditioned manner.

The serotonin molecule has two main active centers, the amino group on the side chain and the hydroxyl group in the 5 position of the indole ring. Two types of derivatives were therefore studied: (1) those in which the amino group was methylated and (2) those in which the hydroxyl group was methylated.

*N-Methyl derivatives*—Two reportedly hallucinogenic compounds with the amino group methylated are bufotenine and psilocybin.

Bufotenine is N,N-dimethylserotonin (figure 1) and is an active component of the psychotropic snuff called *cahoba* used by the Mura Indians of the Rio Negro during their annual assemblies.

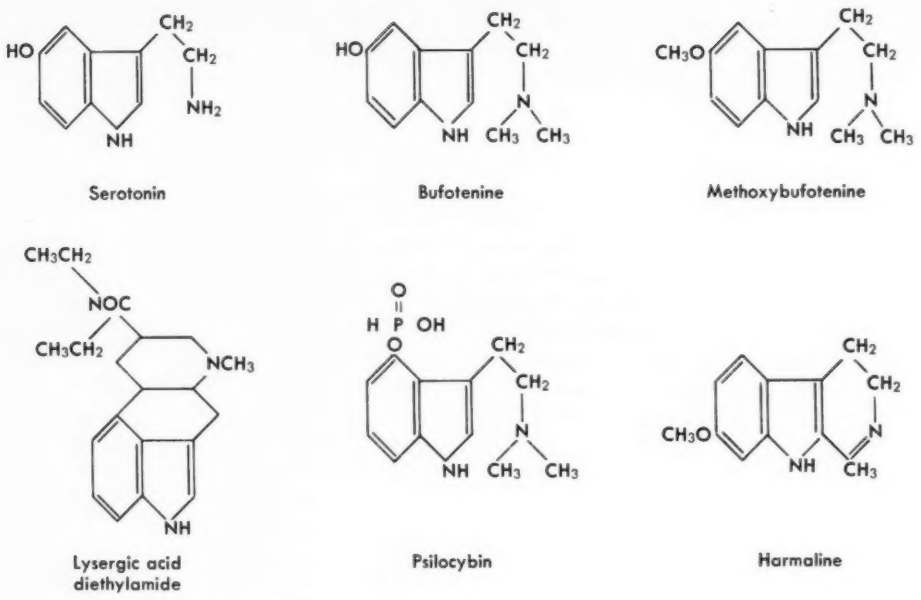



FIGURE 1. Structure of psychotomimetic compounds related to serotonin.

The American ethnologist Gordon Wasson and his wife[13] discovered that the ancient religious rites of the Mazatec Indians in a remote region of Mexico included the eating of *teonanacatl,* the "sacred mushroom," which would induce exhilaration, incoherence and fantastic visions in brilliant colors. Later, these mushrooms (*Psilocybe mexicana* Heim) were successfully cultivated and the psychotropic principle was isolated and identified by Hofmann and others[14] as the phosphoric ester of N-N-dimethyl-4-hydroxytryptamine (figure 1).

Bufotenine and psilocybin were found to be similar to serotonin in their effect on blood pressure. As evidence of their central effect, they potentiated hexobarbital sleeping time to an even greater extent than did serotonin (table 1), a fact that could be correlated to the protection of the amino group from rapid degradation by monoamine oxidase. Thus it seemed that these two hallucinogenic compounds were sufficiently similar structurally to serotonin to mimic some of its actions but sufficiently different from it not to be rapidly metabolized, and thus their actions tended to be more prolonged.[15]

*O-Methyl derivatives*—Epinephrine and norepinephrine are known to be inactivated in the body by methylation of the hydroxyl group. Methylation of hydroxyindoles, in contrast, does not result in inactivation. In a comparative study of a series of serotoninlike compounds and their O-methyl derivatives, it was the methylated compounds that caused trained animals to make the greatest number of mistakes.[16] The O-methyl derivative of serotonin, for example, caused as many mistakes

TABLE 1

PROLONGATION OF SLEEPING TIME BY PSYCHOTOMIMETIC COMPOUNDS

| COMPOUND | AVERAGE SLEEPING TIME (MINUTES) | PROLONGATION (MINUTES) |
|---|---|---|
| Hexobarbital* | 99 ± 14 | |
| Serotonin† | 156 ± 18 | 58 |
| Bufotenine† | 179 ± 13 | 80 |
| Psilocybin† | 224 ± 26 | 125 |

*150 mg. per kilogram.
†51 micromoles per kilogram.

FIGURE 2. The ability of melatonin to lighten the skin of a frog (left).

as bufotenine, and the most potent compound tested in this series was the O-methyl derivative of bufotenine.[16]

*Melatonin*—Since O-methylation appeared to increase psychotomimetic activity, it was of great significance when it was found that this process actually could take place in the brain. As so often happens, this discovery was the result of an endeavor in an entirely different field, namely, the long search by Dr. A. B. Lerner at Yale University for the hormone which can make frog skin lighter in color.

The pineal body has always aroused curiosity, largely because no obvious function could be assigned to it—although according to the Cartesian concept it was reputed to be the seat of the soul. It was, however, known that pineal extracts could cause a lightening in color of the skin of some amphibians. Recently the hormone responsible for this, melatonin, has been isolated by Lerner, Case and Takahashi[17] and found to be the O-methyl derivative of acetylserotonin. It is the most potent skin-lightening agent known (figure 2) and causes the aggregation of melanin granules around the melanocyte nucleus. This aggregation is associated with a change of cytoplasmic colloidal state from a sol to a gel with consequent diminution of melanin production.[18]

Another compound isolated from pineal tissue by the same workers proved to be 5-methoxyindoleacetic acid, and there has been some discussion regarding its origin.

Since these compounds represented a further development in the serotonin story, we synthesized radioactive melatonin and 5-methoxytryptamine to study their metabolic fate. 5-Methoxytryptamine was rapidly metabolized to 5-methoxyindoleacetic acid,[19] whereas only 2 per cent of melatonin was converted to this acid. This seems good circumstantial evidence for the presence of 5-methoxytryptamine in the brain. The significance of the presence of such a physiologically active compound remains to be seen. Melatonin was found to be metabolized largely to 6-hydroxymelatonin[20, 21] but a minor metabolite no longer had the characteristics of an indole compound. Thus the present concept of the complex metabolic pattern of serotonin is best expressed as shown in figure 3. The non-indolic metabolite of melatonin could be explained in three ways: opening of the indole ring, conversion to an oxindole, or cyclization to a harmala alkaloid.

It was the last-named possibility that was particularly intriguing, because the alkaloids are very potent, physiologically active compounds. In the case of melatonin, by the simple removal of one molecule of water it can be converted into 10-methoxyharmalan (figure

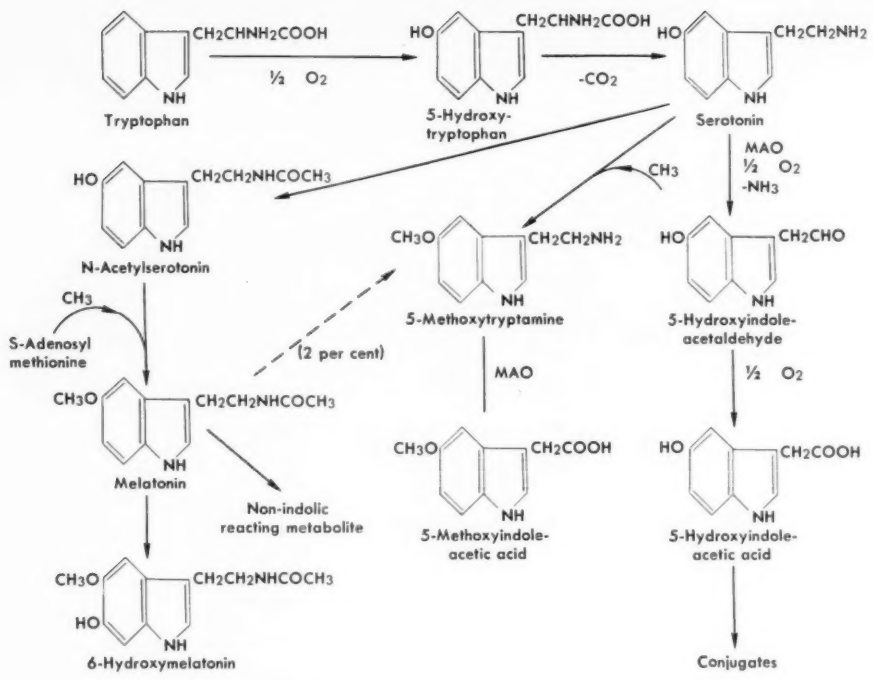



FIGURE 3. Present concept of metabolic pattern of serotonin.

4). Now, melatonin itself appears to have no effect on behavior, but we found that 1 mg. or less of 10-methoxyharmalan given to a trained rat could set it trembling all over and make it quite incapable of correctly performing its simple conditioned behavioral pattern. In addition, 10-methoxyharmalan was found to exert the same skin-lightening effect on frogs as

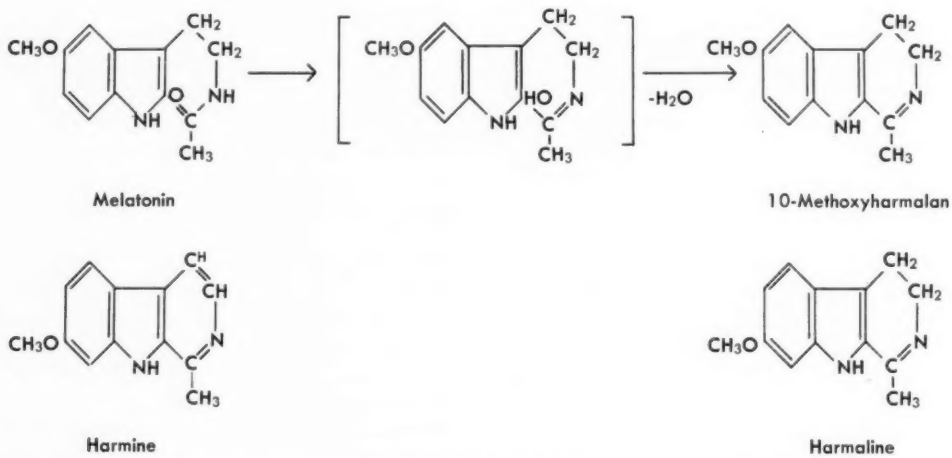



FIGURE 4. Melatonin by cyclodehydration is readily converted into 10-methoxyharmalan, which is related to harmaline.

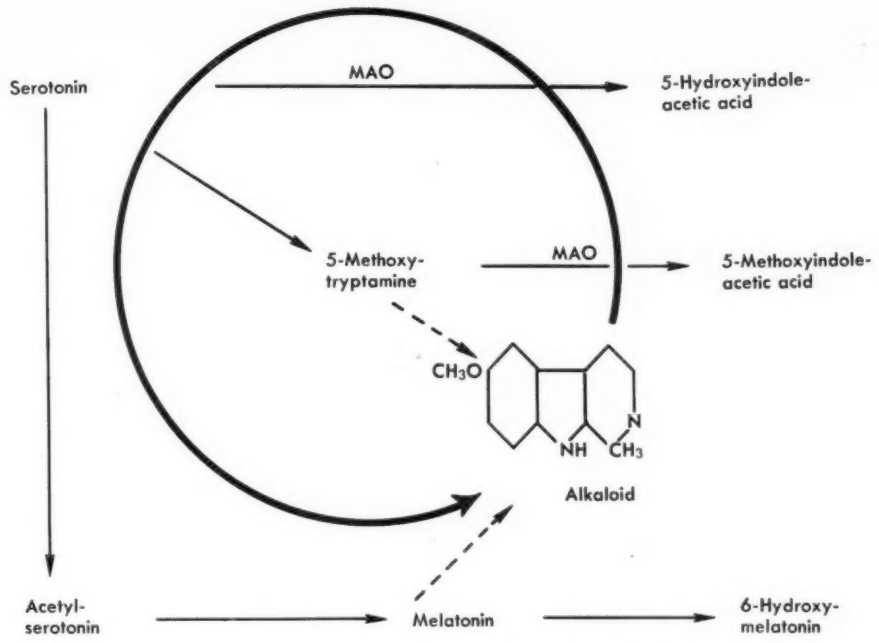



FIGURE 5. Chemical feedback mechanism. The production of an alkaloid would prevent the normal breakdown of serotonin and methoxytryptamine by monoamine oxidase (MAO), thus shunting serotonin metabolism down the pathways to produce more melatonin, methoxytryptamine and alkaloid.

did melatonin, which suggested that some interconversion might take place. Another cogent argument is provided by the fact that in the test tube under physiologic conditions of pH and temperature, amines like 5-methoxytryptamine will condense with aldehydes and keto acids to give a similar harmalan. So it seems quite feasible that under certain circumstances these alkaloids could be produced in the body. The result of such a process could be deduced from the effect 10-methoxyharmalan had on our trained animals and the chemical similarity it bears to harmaline (figure 4), which is the cause of the strange behavior and terrifying hallucinations experienced by the Peruvian Indians after drinking *caapi*.

The psychotomimetic action of LSD has been thought to be due to its ability to block the action of serotonin,[7,8] and it is quite possible that in psychotic states an endogenously produced compound, like LSD, might block the action of serotonin in the brain. It is therefore very significant that recently we have found that 10-methoxyharmalan, itself a derivative of serotonin, is a potent serotonin antagonist. This might well explain the psychotomimetic action of this alkaloid and further emphasize the importance of the possible production of such an abnormal metabolite.

*Chemical feedback mechanism*—The harmala alkaloids, besides causing hallucinations, have another property. They are potent monoamine oxidase inhibitors[22] and could therefore prevent the normal breakdown of serotonin. The formation of such an alkaloid in the body would cause serotonin metabolism to be shunted down the pathways which would lead to the production of more 5-methoxytryptamine, melatonin and 10-methoxyharmalan (figure 5). Thus a chemical feedback mechanism would be set up in which the toxic compound, once formed, would tend to perpetuate its own formation in increasing amounts. On this basis it might be expected that mono-

amine oxidase inhibitors would initiate such a mechanism and, in fact, there have been some reports of hypomania starting with the administration of such drugs and persisting for months after their withdrawal.

## REFERENCES


1. De Ropp, R. S.: Drugs and the Mind. New York, St. Martin's Press, Inc., 1957.
2. Thudichum, J. W. L.: A Treatise on the Chemical Constitution of the Brain. London, Ballière, Tindall and Cox, 1884.
3. Rapport, M. M., Green, A. A. and Page, I. H.: Crystalline serotonin. Science 108:329, 1948.
4. Page, I. H.: Serotonin (5-hydroxytryptamine); the last four years. Physiol. Rev. 38:277, 1958.
5. Twarog, B. M. and Page, I. H.: Serotonin content of some mammalian tissues and urine and method for its determination. Am. J. Physiol. 175:157, 1953.
6. Brodie, B. B. and Shore, P. A.: A concept for a role of serotonin and norepinephrine as chemical mediators in the brain. Ann. New York Acad. Sc. 66:631, 1957.
7. Woolley, D. W. and Shaw, E.: A biochemical and pharmacological suggestion about certain mental disorders. (Abstr.) Science 119:587, 1954.
8. Gaddum, J. H.: Ciba Foundation Symposium on Hypertension. Boston, Little, Brown and Company, 1954.
9. Kety, S. S.: Biochemical theories of schizophrenia. Part I. Science 129:1528, 1959.
10. Udenfriend, S., Titus, E., Weissbach, H. and Peterson, R. E.: Biogenesis and metabolism of 5-hydroxyindole compounds. J. Biol. Chem. 219:335, 1956.
11. Erspamer, V.: Observations on the fate of indolalkylamines in an organism. J. Physiol. 127:118, 1955.
12. McIsaac, W. M. and Page, I. H.: The metabolism of serotonin (5-hydroxytryptamine). J. Biol. Chem. 234:858, 1959.
13. Wasson, V. P. and Wasson, R. G.: Mushrooms, Russia and History. New York, Pantheon Books, Inc., 1957.
14. Hofmann, A., Heim, R., Brack, A. and Kobel, H.: Psilocybin, ein psychotroper Wirkstoff aus dem mexikanischen Rauschpilz Psilocybe mexicana Heim. Experientia 14:107, 1958.
15. Gessner, P. K., Khairallah, P. A., McIsaac, W. M. and Page, I. H.: The relationship between the metabolic fate and pharmacological actions of serotonin, bufotenine and psilocybin. J. Pharmacol. & Exper. Therap. 130:126, 1960.
16. Gessner, P. K., McIsaac, W. M. and Page, I. H.: The pharmacological actions of some methoxyindolealkylamines. Nature, London. (In press.)
17. Lerner, A. B., Case, J. D. and Takahashi, Y.: Isolation of melatonin and 5-methoxyindole-3-acetic acid from bovine pineal glands. J. Biol. Chem. 235: 1992, 1960.
18. Lerner, A. B.: Mechanism of hormone action. Nature, London 184:674, 1959.
19. McIsaac, W. M., Kveder, S. and Page, I. H.: The metabolism of 5-($\beta$-14C) methoxytryptamine. Biochem. J. 76:30p, 1960.
20. Kveder, S., McIsaac, W. M. and Page, I. H.: The metabolism of N-acetyl-5-($\beta$-14C) methoxytryptamine. *Ibid.*,[19] p. 28p.
21. Kopin, I. J., Pare, C. M. C., Axelrod, J. and Weissbach, H.: 6-Hydroxylation, the major metabolic pathway for melatonin. Biochim. et biophys. acta 40:377, 1960.
22. Udenfriend, S., Witkop, B., Redfield, B. G. and Weissbach, H.: Studies with reversible inhibitors of monoamine oxidase: Harmaline and related compounds. Biochem. Pharmacol. 1:160, 1958.


# MEETINGS *and Postgraduate Courses*

American College of Gastroenterology, Cleveland: Annual postgraduate course in gastroenterology, to be held October 26-28 at the Sheraton-Cleveland Hotel. For further information, write to: American College of Gastroenterology, 33 West 60th Street, New York 23.

International Symposium on Bone, San Francisco: Sponsored by the San Francisco Medical Center and Continuing Education in Medicine and the Health Sciences, University of California, and Merck Sharp & Dohme, this symposium will be held October 7-9 in the Medical Sciences Building, University of California Medical Center. For further information, write to: Dr. Seymour M. Farber, Assistant Dean in Charge of Continuing Education in Medicine, University of California Medical Center, San Francisco 22.

Society of Nuclear Medicine, Dallas: Ninth annual meeting to be held June 27-30, 1962, at the Baker Hotel. For further information, write to: Administrator, Society of Nuclear Medicine, 430 North Michigan Avenue, Chicago 11.

University of Minnesota, Minneapolis: Courses to be presented at the Center for Continuation Study during 1961:

Pediatrics for specialists, September 18-21
Obstetrics for specialists, October 2-4
Dermatology for specialists, October 19-21
Radiology for radiologists (urologic radiology), November 6-10
Ophthalmology (refraction) for general physicians, November 15-17
Orthopedics for orthopedic surgeons (hand surgery), November 16-18

For further information, write to: Director, Department of Continuation Medical Education, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14.

# Office Diagnosis of Congenital Malformations of the Heart, Part 1

BENJAMIN M. GASUL, RENE A. ARCILLA AND MAGNUS H. AGUSTSSON*

*Cook County Children's Hospital, Chicago*

*A clinical approach to the diagnosis of congenital cardiac malformations is described which the authors have found effective in exposing the important signs and their significance. Each available diagnostic method is evaluated separately before all data are correlated.*

*Clinical diagnosis based on history, physical examination, roentgenography and electrocardiography was 94 per cent accurate in a series of cases seen in office consultation and 90 per cent accurate in a series of hospital cases reviewed. The significance of the various signs and symptoms that are routinely searched for in the physical examination is discussed.*

*The salient points in the clinical diagnosis of the common entities are presented.*

BENJAMIN M. GASUL

NEVER before in the history of medicine has clinical examination of the cardiac patient been as valuable as it is today. Data obtained by angiocardiography and cardiac catheterization correlated with physical findings, particularly those derived from auscultation, phonocardiography, conventional roentgenograms of the chest, and electrocardiography, and with the lessons learned at the surgical table and at autopsy have revolutionized our knowledge of the hemodynamics of the normal and of the abnormal heart. These correlative studies enable the clinician to recognize and to evaluate properly the timing and significance of the heart sounds and their relation to and the significance of the various types of heart murmurs. Interpretation of roentgenograms also has improved markedly. Roentgenographic findings can be checked by actual angiocardiographic visualization of the structure, the size and position of the cardiac chambers and of the great vessels and their branches, during

*Pediatric Cardiophysiology Department, Cook County Children's Hospital and Hektoen Institute for Medical Research (Dr. Gasul, Director; Dr. Arcilla, Assistant Director; Dr. Agustsson, Research Associate); Department of Pediatrics, University of Illinois College of Medicine (Dr. Gasul, Clinical Professor of Pediatrics; Drs. Arcilla and Agustsson, Clinical Assistant Professors of Pediatrics [Cardiology]); Department of Pediatrics, Presbyterian-St. Luke's Hospital (Dr. Gasul, Attending Physician [Cardiology]), Chicago, Illinois.

RENE A. ARCILLA

MAGNUS H. AGUSTSSON

various phases of systole and diastole. Similarly, information regarding pressures and flows in the cardiac chambers and in the great vessels gained by means of cardiac catheterization has made it possible for the experienced clinician to predict with reasonable accuracy the existing intracardiac pressures or degree of hypertrophy of the ventricles and to a lesser extent of the atria.

### *Clinical Diagnostic Approach*

One of the important activities of the Pediatric Cardiophysiology Department at Cook County Children's Hospital is a research study correlating the clinical, roentgenologic, electrocardiographic, vectorcardiographic, angiocardiographic and hemodynamic data of patients admitted to the service. In the first three or four years of this department's existence the orthodox method of attempting a diagnosis only after the special laboratory procedures had been performed was followed. In the past 10 years this method has been discarded and a new approach has been in use.

The fellow in charge of the case presents initially only the history and the blood pressure in the extremities. Only the staff members and the moderator who are unfamiliar with the case then examine the patient, and each describes his findings. Emphasis is given to the following essential points: presence or absence of cyanosis and of differential cyanosis; presence of distention and pulsations of the veins in the neck; type and rate of respiration; size and location of the heart; presence or absence of enlargement of the individual chambers; character and clinical significance of the first, second, third and fourth sounds; location, intensity and degree of splitting of the first and second sounds; and type, location, frequency and duration of heart murmurs. The members of the staff then discuss the diagnostic possibilities which are based only on the history and the physical findings.

The phonocardiogram, which is always taken by the fellow in charge of the case, is then examined and used to check the validity of the stethoscopic findings. The roentgenograms of the chest are then analyzed without any knowledge of the electrocardiographic tracing to give an unbiased, objective interpretation of roentgenologic findings. For example, if the right ventricle is 100 per cent hypertrophied (i.e., if its wall is 5 to 8 mm. in thickness instead of the normal 3 to 4 mm.), a roentgenogram will not disclose this, but an electrocardiogram almost always will. On the other hand, the chest roentgenogram is superior to the electrocardiogram in terms of recognizing dilatation of the cardiac chambers and great vessels and of evaluating the state of the pulmonary blood flow.

Following analysis of the chest roentgenograms, the electrocardiogram and vectorcardiogram are presented and the diagnostic possibilities are reconsidered. As each laboratory procedure is presented, the criteria and significance of each abnormality are mentioned. The angiocardiograms then are shown, and again those who are aware of the cardiac catheterization data are not allowed to interpret these films. Finally the catheterization findings are discussed, and the moderator then reviews the essential clinical, roentgenologic and electrocardiographic findings and correlates them with the angiocardiographic and hemodynamic data. We believe that each available diagnostic method should be evaluated on its own merits first, before correlation of all data is made. At times a diagnosis based on clinical grounds alone is misleading, but it is also well known that angiocardiographic or cardiac catheterization findings per se confuse the clinician at other times and lead to an incorrect diagnosis.

We have found this clinical approach ex-

tremely effective in exposing the important clinical signs and their physiologic significance. It has been effective in teaching our fellows and ourselves, and even the young staff members become quite proficient in clinical diagnosis in a relatively short time.

### *Accuracy of Clinical Diagnosis in 476 Cases*

The purpose of this paper is to present actual data on the value and limitations of the diagnosis of congenital malformations of the heart based on physical examination, roentgenography and electrocardiography. Since usually only very complicated and rare cases are reported in the literature, and since these cases usually cannot be diagnosed correctly on clinical grounds alone or even by all available laboratory studies, one gets an erroneous impression of the true value of clinical diagnosis.

We have reviewed the clinic records of 296 consecutive patients with congenital heart disease seen in office consultation in 1959 (table 1) and the hospital records of 180 consecutive patients admitted to the cardiology ward in the same year. The diagnosis was established in 129 of the office cases and in 155 of the hospital cases by angiocardiography, aortography, cardiac catheterization, surgery or postmortem findings (tables 2 and 3). The preliminary diagnosis based on clinical findings alone aided by fluoroscopic or roentgenographic examination of the chest, or both, and by 15-lead electrocardiograms was compared with the final established diagnosis. The original clinical diagnosis was confirmed by subsequent special studies in 94 per cent of the office cases and in 90 per cent of the hospital cases (tables 2 and 3).

The following entities, in order of frequency, accounted for about 90 per cent of the cases seen in the office: ventricular septal defect, innocent murmur, tetralogy of Fallot, atrial septal defect, pulmonary stenosis with intact ventricular septum, aortic stenosis, patent ductus arteriosus, transposition of the great vessels, Ebstein's anomaly, and coarctation of the aorta. Of the hospital cases, the following entities, again in order of frequency, caused about 90 per cent: ventricular septal defect, tetralogy of Fallot, fibroelastosis, patent ductus arteriosus, common atrioventricular canal, pulmonary stenosis with intact ventricular septum, aortic stenosis, ventricular septal defect and pulmonary stenosis, ventricular septal defect and patent ductus arteriosus,

TABLE 1

PATIENTS WITH CONGENITAL MALFORMATIONS OF THE HEART SEEN IN OFFICE CONSULTATION IN 1959

| ENTITY | NUMBER | PER CENT |
|---|---|---|
| Ventricular septal defect | 83 | 28 |
| Innocent murmur | 52 | 17.5 |
| Tetralogy of Fallot | 26 | 8.8 |
| Atrial septal defect (ostium secundum 24, ostium primum 2) | 26 | 8.8 |
| Isolated pulmonary stenosis | 26 | 8.8 |
| Aortic stenosis | 21 | 7.0 |
| Patent ductus arteriosus | 12 | 4.0 |
| Complete transposition of great vessels | 5 | 1.7 |
| Ebstein's anomaly | 5 | 1.7 |
| Coarctation of aorta | 4 | 1.35 |
| Congenital aortic regurgitation | 3 | 1.0 |
| Coarctation of pulmonary artery | 3 | 1.0 |
| Fibroelastosis | 3 | 1.0 |
| Atrial septal defect and ventricular septal defect with pulmonary hypertension | 3 | 1.0 |
| Pulmonary stenosis with atrial septal defect | 3 | 1.0 |
| Tricuspid atresia | 2 | 0.7 |
| Ventricular septal defect and patent ductus arteriosus | 2 | 0.7 |
| Total anomalous pulmonary venous connection | 2 | 0.7 |
| Marfan's syndrome with aortic sinus aneurysm | 2 | 0.7 |
| Idiopathic dilatation of pulmonary artery | 2 | 0.7 |
| Coarctation of aorta and ventricular septal defect | 1 | 0.35 |
| Coarctation of aorta and aortic regurgitation | 1 | 0.35 |
| Preductal coarctation of aorta | 1 | 0.35 |
| Single ventricle | 1 | 0.35 |
| Coarctation of aorta and aortic stenosis | 1 | 0.35 |
| Atrioventricularis communis or ventricular septal defect | 1 | 0.35 |
| Pulmonary stenosis with ventricular septal defect | 1 | 0.35 |
| Eisenmenger's complex | 1 | 0.35 |
| Cor triatriatum | 1 | 0.35 |
| Aberrant thoracic arteries to right lung with arteriovenous fistula | 1 | 0.35 |
| Taussig-Bing anomaly | 1 | 0.35 |
| | 296 | 100 |

TABLE 2

ESTABLISHED DIAGNOSES IN 129 OFFICE CASES

| ENTITY | ESTABLISHED DIAGNOSIS | CORRECT CLINICAL DIAGNOSIS | INCORRECT CLINICAL DIAGNOSIS | SPECIAL STUDIES | | | |
|---|---|---|---|---|---|---|---|
| | | | | *Catheterization* | *Angiocardiography* | *Surgery* | *Autopsy* |
| Ventricular septal defect | 25 | 24 | 1 | 25 | 3 | 14 | 3 |
| Tetralogy of Fallot | 16 | 16 | 0 | 11 | 11 | 15 | 4 |
| Atrial septal defect | 20 | 20 | 0 | 20 | 1 | 18 | 1 |
| Pulmonary stenosis | 18 | 18 | 0 | 18 | 1 | 7 | 0 |
| Patent ductus arteriosus | 7 | 7 | 0 | 0 | 0 | 7 | 0 |
| Aortic stenosis | 6 | 6 | 0 | 5 | 1 | 4 | 2 |
| Complete transposition of great vessels | 6 | 5 | 1 | 0 | 5 | 3 | 1 |
| Ebstein's anomaly | 3 | 3 | 0 | 3 | 1 | 2 | 1 |
| Coarctation of aorta | 3 | 3 | 0 | 2 | 2 | 2 | 0 |
| Atrial septal defect and ventricular septal defect with pulmonary hypertension | 3 | 3 | 0 | 3 | 1 | 2 | 0 |
| Pulmonary stenosis with atrial septal defect | 3 | 2 | 1 | 3 | 1 | 1 | 0 |
| Coarctation of pulmonary artery | 2 | 2 | 0 | 2 | 0 | 0 | 0 |
| Tricuspid atresia | 2 | 2 | 0 | 0 | 1 | 2 | 1 |
| Ventricular septal defect and patent ductus arteriosus | 2 | 1 | 1 | 2 | 0 | 2 | 0 |
| Total anomalous pulmonary venous drainage | 2 | 2 | 0 | 2 | 2 | 1 | 0 |
| Marfan's syndrome with aortic sinus aneurysm | 2 | 2 | 0 | 1 | 2 | 0 | 1 |
| Congenital aortic regurgitation | 1 | 1 | 0 | 1 | 1 | 0 | 0 |
| Coarctation of aorta and ventricular septal defect | 1 | 1 | 0 | 1 | 0 | 1 | 0 |
| Coarctation of aorta and aortic regurgitation | 1 | 1 | 0 | 1 | 1 | 1 | 0 |
| Preductal coarctation of aorta | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| Coarctation of aorta and aortic stenosis | 1 | 1 | 0 | 1 | 0 | 1 | 1 |
| Pulmonary stenosis with ventricular septal defect | 1 | 1 | 0 | 1 | 0 | 0 | 0 |
| Eisenmenger's complex | 1 | 1 | 0 | 1 | 0 | 0 | 0 |
| Cor triatriatum | 1 | 0 | 1 | 0 | 1 | 1 | 1 |
| Aberrant systemic artery to right lung | 1 | 0 | 1 | 0 | 1 | 1 | 0 |
| | 129 | 122 | 7 | 103 | 37 | 85 | 16 |

Taussig-Bing anomaly, coarctation of the aorta, coarctation of the pulmonary artery, tricuspid atresia, Marfan's syndrome with aortic sinus aneurysm, and atrial septal defect. Almost all these entities can be diagnosed clinically. Table 4 lists the entities that were not correctly diagnosed clinically.

A *sine qua non* for a successful clinical examination is a quiet room that is well illuminated, preferably by natural light. Full cooperation of the patient also is important. We find it necessary to sedate many infants and children less than three years old with NEMBUTAL® or SECONAL®, using approximately 0.1 gr. per pound of body weight dissolved in 3 to 5 cc. of water and administered rectally. If the patient is not well sedated after 30 minutes, it may be necessary to give an additional amount of sedative (one-fourth or one-third of the initial dose).

### *Significance of Various Clinical Signs and Symptoms*

Before we discuss separately the common congenital malformations of the heart, a brief discussion of the significance of the clinical signs and symptoms that are searched for routinely during the physical examination is in order.

Cyanosis of cardiac origin is due to shunting of venous blood into the systemic circulation through any intracardiac defect or abnormal communication between the lesser and systemic circulations or between the pulmonary arteries and pulmonary veins. Peripheral cyanosis results from an abnormal slowing of the blood flow in the small vessels and capillaries with consequent desaturation of the hemoglobin. This is commonly noted in patients with severe congestive heart failure. Cyanosis also may be due to inadequate oxygenation in the lungs such as in extensive atelectasis, pneumonia, large diaphragmatic hernia, or other conditions interfering with pulmonary ventilation.

"Differential cyanosis" refers to a significant discrepancy in the degree of cyanosis between different segments of the body, notably the upper and the lower extremities. When the lower extremities are definitely more cyanotic than the upper extremities, a ductus with reversed flow is assumed to exist. When the upper extremities are remarkably more cyanotic than the lower extremities, complete transposition of the great vessels accompanied by a patent ductus arteriosus probably exists. This is explained by the fact that the shunt arising from the pulmonary artery is fully oxygenated, and this lessens the arterial unsaturation of the lower part of the body compared with the upper extremities. Although the degree of cyanosis of the upper and lower extremities usually is identical, occasionally patients with tetralogy or tricuspid atresia who have equivalent arterial unsaturation of all extremities may manifest some differences in color of the fingers and toes, the latter appearing somewhat less cyanotic than the former. The explanation for this is not known; sometimes it is due to peripheral vasoconstriction when the feet are exposed to the cold.

Patients with excessive pulmonary blood flow usually have frequent respiratory infections, poor growth and development, easy fatigability and exertional dyspnea. They frequently manifest tachypnea even at rest. These findings may be noted in acyanotic patients with marked left-to-right shunts, such as in ventricular septal defect, patent ductus arteriosus, large atrial septal defect, or aortic-pulmonary septal defect, or in cyanotic patients with marked pulmonary blood flow, as in transposition of the great vessels without pulmonary stenosis, total anomalous pulmonary venous connection, or common atrioventricular canal. A forceful and localized apical impulse that is displaced laterally and downward ordinarily suggests left ventricular enlargement. A diffuse precordial impulse and left lower parasternal lift, which may be accompanied by a precordial bulge, strongly indicate right ventricular enlargement. When there is no myocardial or valvular disease, the degree of cardiac enlargement is a good index of the approximate magnitude of the pulmonary blood flow due to left-to-right shunts. Other findings associated with excessive pulmonary blood flow are a loud first sound due to forceful atrioventricular valvular closure and a mid-diastolic rumble at or inside the apex due to torrential, turbulent blood flow through the atrioventricular orifice in early diastole.

Much information may be derived from the second sound, which in the pediatric age group is normally loudest at the pulmonary area and is normally split, the aortic valvular closure preceding the pulmonary closure. The splitting normally becomes wider on inspiration due to increased systemic venous return to the right chambers, which prolongs the right ventricular systole and thus delays closure of the pulmonary valve, whereas the splitting becomes narrower or may even disappear on expiration. A widely split second sound is due to a marked delay in closure of the pulmonary valve. It occurs in prolonged mechanical systole of the right ventricle from overfilling, as in atrial septal defect, or from obstruction to right ventricular ejection, as in

TABLE 3

ESTABLISHED DIAGNOSES IN 155 HOSPITAL CASES

| ENTITY | ESTABLISHED DIAGNOSIS | CORRECT CLINICAL DIAGNOSIS | INCORRECT CLINICAL DIAGNOSIS | SPECIAL STUDIES | | | |
|---|---|---|---|---|---|---|---|
| | | | | *Catheterization* | *Angiocardiography* | *Surgery* | *Autopsy* |
| Ventricular septal defect | 41 | 40 | 1 | 37 | 40 | 8 | 3 |
| Tetralogy of Fallot | 23 | 23 | 0 | 20 | 23 | 17 | 6 |
| Fibroelastosis | 14 | 14 | 0 | 6 | 14 | 0 | 1 |
| Patent ductus arteriosus | 11 | 11 | 0 | 10 | 10 | 7 | 0 |
| Common atrioventricular canal | 7 | 6 | 1 | 4 | 7 | 0 | 2 |
| Isolated pulmonary stenosis | 6 | 6 | 0 | 5 | 6 | 2 | 0 |
| Aortic stenosis | 4 | 4 | 0 | 3 | 4 | 2 | 2 |
| Ventricular septal defect and pulmonary stenosis | 4 | 3 | 1 | 3 | 4 | 0 | 0 |
| Ventricular septal defect and patent ductus arteriosus | 3 | 3 | 0 | 3 | 3 | 1 | 0 |
| Taussig-Bing anomaly | 3 | 2 | 1 | 3 | 3 | 1 | 2 |
| Coarctation of aorta | 3 | 3 | 0 | 1 | 3 | 2 | 1 |
| Coarctation of pulmonary artery | 3 | 1 | 2 | 3 | 3 | 0 | 0 |
| Tricuspid atresia | 3 | 3 | 0 | 3 | 3 | 2 | 2 |
| Marfan's syndrome with aortic sinus aneurysm | 3 | 3 | 0 | 2 | 3 | 0 | 0 |
| Atrial septal defect | 2 | 2 | 0 | 2 | 1 | 1 | 0 |
| Truncus communis | 2 | 2 | 0 | 1 | 2 | 0 | 0 |
| Normal heart; innocent murmur | 2 | 2 | 0 | 1 | 2 | 0 | 0 |
| Patent ductus arteriosus and coarctation of pulmonary artery | 2 | 2 | 0 | 2 | 2 | 1 | 0 |
| Ebstein's anomaly | 1 | 1 | 0 | 1 | 1 | 1 | 0 |
| Coronary arteriovenous fistula | 1 | 1 | 0 | 1 | 1 | 1 | 0 |
| Atrial septal defect and coarctation of pulmonary artery | 1 | 0 | 1 | 1 | 1 | 0 | 0 |
| Pulmonary stenosis and coarctation of pulmonary artery | 1 | 0 | 1 | 1 | 1 | 0 | 0 |

isolated pulmonary valvular or infundibular stenosis. Fixed or constant splitting is nearly characteristic of atrial septal defect, as the increment in the systemic venous return to the right atrium tends to limit the shunt from the left atrium. Wide splitting of the second sound also may be due to delayed electric systole of the right ventricle, as in complete right bundle-branch block. Absence of splitting of the second sound is not infrequent in tachycardia, due to the nearly simultaneous closure of the aortic and pulmonic valves. An easily palpable and very loud second sound which is closely split or single almost always indicates marked pulmonary hypertension. Single second sounds also occur in entities with only one set of semilunar valves, as in truncus communis, and in those with atresia of either the aortic or the pulmonary orifice. In most cases of tetralogy of Fallot, only a single second sound (aortic valve closure) is present, since low pressure in the pulmonary artery and deficient pulmonary blood flow produce an inaudible pulmonary valvular closure sound.

Whenever left ventricular systole is markedly prolonged so that the aortic valve closes after the pulmonary valve (the reverse of the normal time relationship), the so-called paradoxical splitting occurs and the examiner notes this splitting during expiration instead of during inspiration. During expiration the

TABLE 3 *(Continued)*

ESTABLISHED DIAGNOSES IN 155 HOSPITAL CASES

| ENTITY | ESTABLISHED DIAGNOSIS | CORRECT CLINICAL DIAGNOSIS | INCORRECT CLINICAL DIAGNOSIS | SPECIAL STUDIES | | | |
|---|---|---|---|---|---|---|---|
| | | | | *Catheterization* | *Angiocardiography* | *Surgery* | *Autopsy* |
| Preductal coarctation, aortic stenosis, fibroelastosis | 1 | 0 | 1 | 0 | 0 | 0 | 1 |
| Aortic regurgitation | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| Hypoplastic right ventricle, atrial septal defect | 1 | 0 | 1 | 1 | 1 | 1 | 0 |
| Transposition of great vessels, pulmonary stenosis | 1 | 0 | 1 | 1 | 1 | 1 | 0 |
| Pseudotruncus; levocardia | 1 | 1 | 0 | 1 | 1 | 0 | 0 |
| Ventricular septal defect, coarctation of pulmonary artery | 1 | 0 | 1 | 1 | 1 | 0 | 1 |
| Patent ductus arteriosus, atrial septal defect | 1 | 0 | 1 | 1 | 1 | 1 | 0 |
| Tricuspid atresia, transposition of great vessels | 1 | 1 | 0 | 1 | 1 | 0 | 1 |
| Coarctation of aorta, patent ductus arteriosus | 1 | 1 | 0 | 0 | 1 | 0 | 1 |
| Total anomalous pulmonary venous connection | 1 | 1 | 0 | 1 | 1 | 1 | 0 |
| Mirror-image dextrocardia | 1 | 1 | 0 | 1 | 1 | 0 | 0 |
| Mesoversion, transposition of great vessels, pulmonary stenosis | 1 | 1 | 0 | 1 | 1 | 0 | 0 |
| Dextroversion, transposition of great vessels, pulmonary stenosis | 1 | 0 | 1 | 1 | 1 | 1 | 0 |
| Congenital aplasia of right ventricular myocardium | 1 | 0 | 1 | 1 | 1 | 0 | 0 |
| Congenital mitral regurgitation, ventricular septal defect | 1 | 0 | 1 | 1 | 1 | 0 | 0 |
| | 155 | 139 | 16 | 125 | 151 | 51 | 23 |

splitting becomes wider, since the pulmonary valve closes ahead of the aortic valve, while during inspiration, with the pulmonic valve closure normally being delayed, the closure of both valves occurs almost simultaneously. We have noted this in severe aortic stenosis, in patent ductus arteriosus with large left-to-right shunt, and in complete left bundle-branch heart block.

An audible third heart sound is normal in the pediatric age group unless it is unusually loud and widely distributed. An audible fourth heart sound is always abnormal. This sound appears to be related to increased resistance to atrial emptying, as may be seen in tricuspid atresia or stenosis, severe pulmonary stenosis, pulmonary hypertension, and in similar lesions involving the left heart chambers. Prominent "a" wave pulsations in the neck veins sometimes may be present in these conditions. In pronounced first-degree atrioventricular block the fourth heart sound may be recorded in the phonocardiogram and may even be audible; it does not, however, signify any of the previously named conditions.

### *Acyanotic Congenital Malformations of the Heart;*
### *1. Ventricular Septal Defect*

In our experience, ventricular septal defect is the most common acyanotic congenital malformation of the heart. The size rather than

TABLE 4

ENTITIES INCORRECTLY DIAGNOSED*

| CLINICAL DIAGNOSIS | CORRECT DIAGNOSIS |
|---|---|
| *Office cases:* | |
| Transposition of great vessels | Preductal coarctation of aorta |
| Isolated pulmonary stenosis | Pulmonary stenosis with atrial septal defect |
| Atrioventricularis communis | Ventricular septal defect with pulmonary hypertension |
| Ventricular septal defect (misdiagnosed also by all tests) | Ventricular septal defect with patent ductus arteriosus (diagnosed at surgery) |
| Total anomalous pulmonary venous drainage | Cor triatriatum |
| Aortic valvular or subvalvular stenosis | Aortic supravalvular stenosis |
| Pulmonary arteriovenous fistula | Aberrant thoracic arteries to right lung with arteriovenous fistula |
| *Hospital cases:* | |
| Innocent murmur | Coarctation of right pulmonary artery |
| Isolated pulmonary stenosis | Pulmonary stenosis with coarctation of right pulmonary artery |
| Isolated pulmonary stenosis | Coarctation of both pulmonary arteries |
| Ventricular septal defect; pulmonary stenosis | Ventricular septal defect; coarctation of both pulmonary arteries |
| Ventricular septal defect; atrial septal defect | Common atrioventricular canal |
| Eisenmenger's complex | Taussig-Bing anomaly |
| Tetralogy of Fallot | Complete transposition of great vessels; pulmonary stenosis |
| Patent ductus arteriosus; ventricular septal defect | Patent ductus arteriosus; atrial septal defect |
| Aortic stenosis; fibroelastosis | Preductal coarctation; subaortic stenosis; fibroelastosis |
| Tricuspid stenosis; ventricular septal defect | Hypoplastic right ventricle; atrial septal defect |
| Common atrioventricular canal | Ventricular septal defect |
| Atrial septal defect | Atrial septal defect; coarctation of left pulmonary artery |
| Congenital mitral regurgitation | Congenital mitral regurgitation; ventricular septal defect |
| Dextroversion; tetralogy | Dextroversion; transposition of great vessels; ventricular septal defect; pulmonary stenosis |
| Ebstein's anomaly | Congenital aplasia of right ventricular myocardium |

*The differential diagnosis of these entities will be discussed by the authors in another article.

the location of the defect appears to be the critical factor responsible for the varying hemodynamics and clinical manifestations. This entity may be divided into four groups, based on the amount of shunt through the defect and on the pulmonary arterial pressure.

In group 1 the septal defect is small, the shunt is small, and pulmonary arterial pressure is normal. The patients are asymptomatic, and aside from a harsh pansystolic murmur, often accompanied by a thrill and of maximal intensity at the third and fourth left intercostal spaces, the heart size, heart tones, chest roentgenograms and electrocardiograms are within normal limits. In rare instances when the defect is at the lower muscular septum, the murmur is "puffy," not pansystolic, and has an ejection character with midsystolic accentuation. The murmur in these unusual cases tends to diminish, and in a few cases that we have followed it has even disappeared completely over a period of several years.

In group 2 a larger left-to-right shunt and mild to moderate pulmonary hypertension exist. The majority of patients are relatively asymptomatic. Slight cardiac enlargement is present, and is accompanied by a harsh pansystolic murmur and thrill of maximal intensity at the fourth and third left interspaces (figure 1a). The second sound is somewhat accentuated and is split. A third sound is present, often followed by a short apical middiastolic rumble. Chest roentgenograms reveal some increase in pulmonary vascular markings and moderate cardiac enlargement, principally of the left ventricle. The electrocardio-

gram shows left ventricular hypertrophy.

In group 3 a large left-to-right shunt and at times a small right-to-left shunt and moderate to severe pulmonary hypertension are present. The patients have frequent respiratory infections, retarded physical development, fatigability and exertional dyspnea. Cardiac enlargement is marked, accompanied by a forceful and hyperactive apical impulse and left lower parasternal lift suggesting biventricular enlargement. A localized pulsation and increased dullness at the pulmonary area may be present which suggest dilatation of the pulmonary trunk. Although the murmur often is still pansystolic, at times it is shorter in duration. The first and split second heart sounds are unusually loud, and a prolonged mid-diastolic rumble at and inside the apex usually is present (figure 1b). Fluoroscopic study and roentgenograms of the chest reveal pulmonary plethora with increased pulsations not only of the primary and secondary pulmonary arterial branches but also of the tertiary branches in the middle third of the lung fields, a dilated pulmonary trunk, and marked cardiac enlargement involving all chambers. The electrocardiogram reveals left atrial hypertrophy and biventricular (but usually predominantly left ventricular) hypertrophy. Patients in this group are prone to congestive heart failure but usually respond favorably to careful medical management. The majority improve considerably after the first or second year of life. This is the group of patients in whom surgical intervention is required.

In group 4 (Eisenmenger's complex) the large septal defect is complicated by the presence of extensive pulmonary vascular changes producing high pulmonary resistance and hypertension which result in a bidirectional (predominantly right-to-left) shunt. Since these pulmonary vascular changes take many years to develop, this group actually represents a later stage in the history of patients with large ventricular septal defects. Patients in this group usually are in the second, third or fourth decade of life. Mild to moderate cyanosis is present, and the symptoms previously related to increased pulmonary blood flow are absent. The heart is only moderately

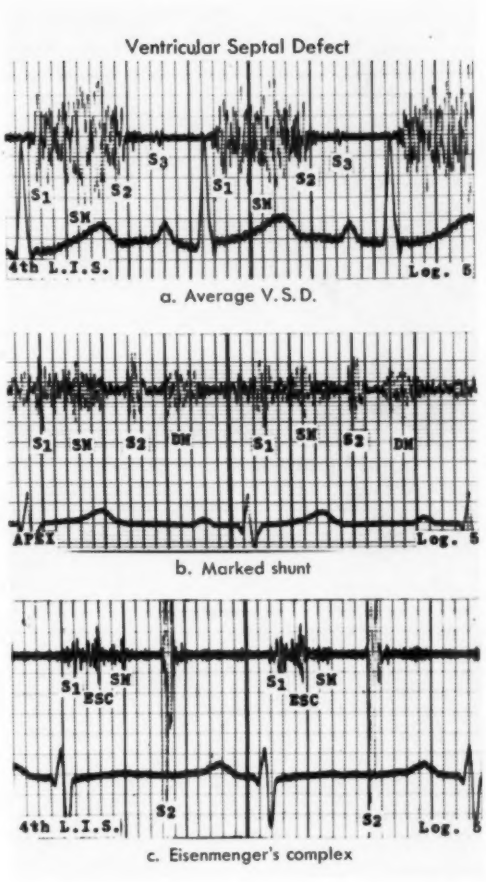



FIGURE 1. Phonocardiograms in ventricular septal defect.

a. Thirteen year old girl with moderately large defect (pulmonary arterial pressure 42/12 mm. Hg; left-to-right shunt 4.4 liters/minute/$M^2$). Note pansystolic murmur (SM) and constant third heart sound ($S_3$).

b. Six year old girl with large defect (pulmonary arterial pressure 92/57 mm. Hg, femoral arterial pressure 97/72 mm. Hg; left-to-right shunt 10.4 liters/minute/$M^2$). Note loud diastolic murmur at apex (DM) in addition to the systolic murmur which has a midsystolic accentuation (SM).

c. Twelve year old girl with large defect and extensive pulmonary vascular changes (pulmonary arterial pressure 108/73 mm. Hg, femoral arterial pressure 108/73 mm. Hg; right-to-left shunt 2.7 liters/minute/$M^2$, left-to-right shunt 0.9 liter/minute/$M^2$). Note the short, faint systolic murmur (SM), the unusually loud second sound ($S_2$) and the early systolic click (ESC).

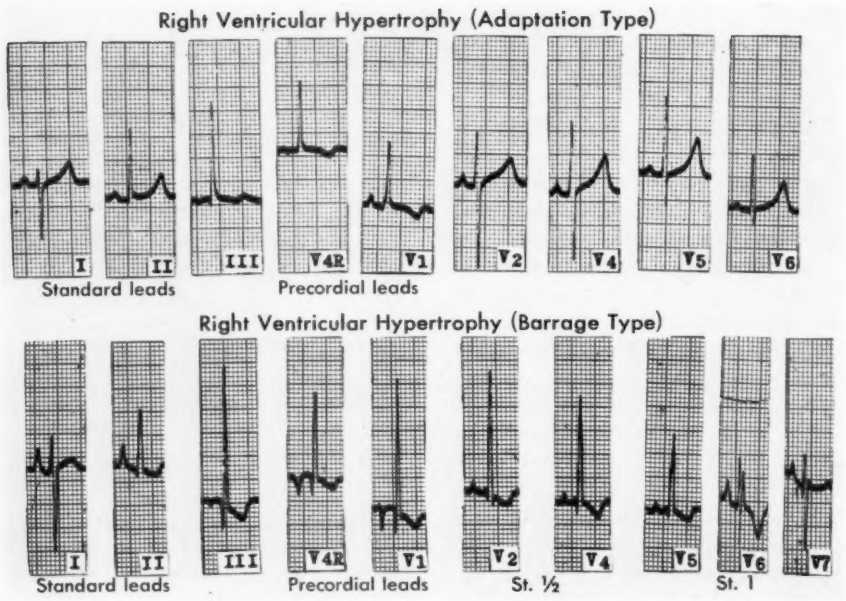



FIGURE 2. *Upper tracing:* Electrocardiogram of patient with tetralogy of Fallot showing the adaptation type of right ventricular hypertrophy. *Lower tracing:* Electrocardiogram of patient with severe isolated pulmonary stenosis showing the barrage type of right ventricular hypertrophy.

The frontal QRS axis in both tracings is similar. In the precordial tracings of the adaptation type (where the right ventricular pressure approximates that of the left ventricle) there is a sudden change in the QRS pattern from an rsR′ pattern in $V_{4R}$ through $V_1$ to an rS pattern in $V_2$. In the barrage type (where the right ventricular pressure is much higher than that of the left ventricle) the QRS complex consisting of a tall R wave and no S wave, accompanied by the negative T waves, is present in $V_{4R}$ through $V_6$.

enlarged, and this is due to right ventricular enlargement as manifested by a left lower parasternal lift and usually also a precordial bulge. A grade 2 or 3, soft, short and early ejection systolic murmur is present at the second and third left intercostal spaces followed by a palpable, loud, closely split or single second sound at the pulmonary area. An early systolic ejection click immediately following the first sound is common (figure 1c). Roentgenologic examination reveals dilatation and marked pulsation of the pulmonary trunk and primary branches and nearly normal vascular markings in the middle third of the lung field. The electrocardiogram shows right atrial and right ventricular hypertrophy of the adaptation type (figure 2, upper tracing). Rarely these clinical findings may be noted in infants or young children; in our experience, they have been due to ventricular septal defects complicated by other anomalies, notably some form of transposition complex.

### *2. Patent Ductus Arteriosus*

Patent ductus arteriosus is an abnormal arterial communication between the proximal portion of the left pulmonary artery and the aorta just distal to the site of origin of the left subclavian artery. The vast majority of patients are asymptomatic but the lesion can be fatal even in infancy. Clinical findings vary depending on the size of the shunt and on the pulmonary arterial pressure and resistance. Four categories of patients will be considered in discussing this entity:

Group 1—Patients with left-to-right shunts only, whose pulmonary arterial pressures are normal or moderately increased.

Group 2—Patients with large left-to-right shunts whose pulmonary arterial pressures are

markedly increased but whose pulmonary resistance is normal or slightly elevated.

Group 3—Patients with bidirectional shunts whose pulmonary arterial pressures and vascular resistance are high.

Group 4—Patients with right-to-left shunts whose pulmonary pressures and resistance are at or above systemic levels.

Group 1 is by far the most common. If the shunt is small, the patient is asymptomatic. The characteristic clinical finding is a loud, continuous (machinery) murmur maximal in the first and second left interspaces, often accompanied by a thrill. The typical murmur has late systolic accentuation and early diastolic fall, so that the second sound is enveloped in the murmur (figure 3a) and can be recognized distinctly only at the lower precordial area. The systolic component of this murmur may be heard over most of the precordium. These patients have normal-sized hearts, and the pulmonary vascular markings on the chest roentgenograms appear within normal limits, although the pulmonary artery may be enlarged slightly. The electrocardiogram either is within normal limits or shows slight left ventricular hypertrophy. In the presence of a larger left-to-right shunt the patient may have fatigability and dyspnea on exertion, and even growth retardation. These patients often have bounding pulses and widened pulse pressures. The heart is somewhat enlarged and the apical impulse is hyperdynamic. A third heart sound and an apical mid-diastolic rumble usually are present. Fluoroscopic study and roentgenograms of the chest reveal an enlarged left atrium and left ventricle, dilatation and pulsation of the pulmonary trunk and branches, and increased pulmonary vascular markings. The electrocardiogram shows left atrial hypertrophy and left ventricular hypertrophy of the diastolic overloading pattern.

Most of the patients in group 2 are infants, who often are seriously ill and may even die if untreated. A continuous murmur usually is still present, but the diastolic component tends to end much earlier; in exceptional cases only a loud systolic murmur, frequently with late systolic accentuation, may be present at

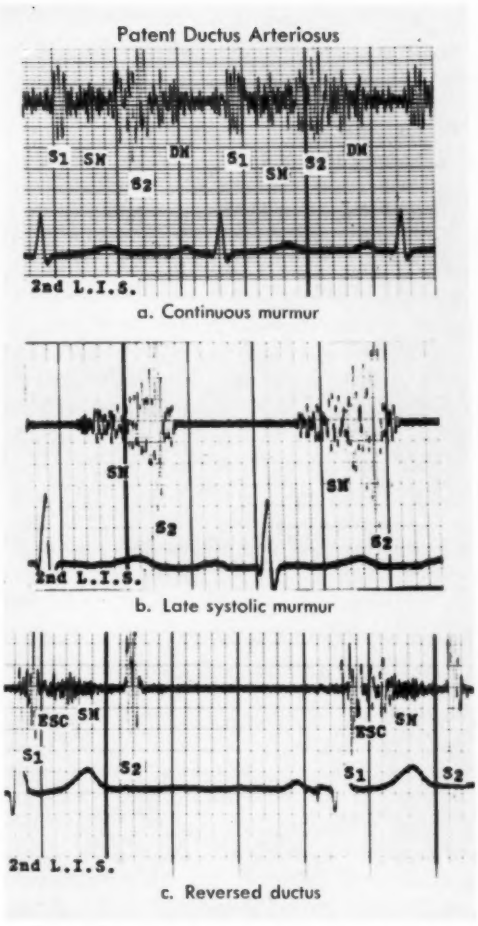



FIGURE 3. Phonocardiograms in patent ductus arteriosus.

a. Typical continuous murmur showing crescendo systolic (SM) and decrescendo diastolic (DM) components. The second heart sound is enveloped in the murmur.

b. Tracing of a 16 month old boy with congestive heart failure and a large patent ductus arteriosus (left-to-right shunt 12 liters/minute/$M^2$; pulmonary arterial pressure 100/50 mm. Hg, aortic pressure 140/50 mm. Hg). Note crescendo late-systolic murmur (SM) and loud second heart sound ($S_2$).

c. Tracing of a five year old girl with reversed flow through a large patent ductus arteriosus (right-to-left shunt 1.2 liters/minute/$M^2$, left-to-right shunt 0.5 liter/minute/$M^2$; pulmonary arterial pressure 100/61 mm. Hg, aortic pressure 112/56 mm. Hg). Note the faint systolic murmur (SM), the early systolic click (ESC) and the loud second heart sound ($S_2$).

the pulmonary area and suprasternal notch (figure 3b). In our experience a high pulse pressure is present in these cases, and this is of considerable value in distinguishing the entity from a large ventricular septal defect. The use of systemic pressor agents, such as mephentermine sulfate (WYAMINE® sulfate) or inhalation of 100 per cent oxygen for several minutes by mask (or both these measures) often brings out the early diastolic murmur. The first sound is accentuated and the second sound is closely split and loud; in rare instances it may manifest paradoxical splitting due to the markedly delayed aortic valvular closure. A loud third sound and a mid-diastolic rumble inside the apex usually are present. Roentgenograms show considerable cardiomegaly with left atrial and left and right ventricular enlargement, large pulmonary arteries, and increased pulmonary vascular markings. The electrocardiogram shows left atrial hypertrophy and biventricular hypertrophy. Since surgical treatment is indicated, it is essential to establish the correct diagnosis. In the very few cases in which the diagnosis is doubtful, angiocardiography or cardiac catheterization is definitely indicated.

The third group of patients usually have dyspnea on exertion, fatigability, and latent cyanosis on exertion. Peripheral pulses and pulse pressures usually are normal. The heart is moderately enlarged, and a lower parasternal lift and palpable second sound at the pulmonary area are present. A grade 3, ejection-type systolic murmur at the pulmonary area which is easily transmitted to the back and a loud, single or closely split second sound at the pulmonic area are present. An early systolic click is commonly noted at the base and lower precordium (figure 3c). These findings may be accompanied by a high-pitched, decrescendo, early diastolic murmur in the same area due to pulmonic regurgitation. Roentgenologic examination reveals moderate enlargement of the heart with more evidence of right ventricular than of left ventricular enlargement, dilatation and marked pulsation of the pulmonary trunk and primary and secondary branches, and normal or slightly increased vascular markings in the middle third of the lung field. The electrocardiogram shows right ventricular hypertrophy of the adaptation type (figure 2, upper tracing) and, rarely, biventricular hypertrophy.

The fourth group is a very small one. Primary pulmonary hypertension appears to be the essential lesion, and the associated patent ductus arteriosus merely functions as an escape mechanism for the excessive pulmonary hypertension and vascular resistance. Clinically these children present the same findings as the third group, and in addition may show cyanosis of significantly more severe degree in the lower extremities and left fingers compared with the right fingers, which are only slightly cyanotic if at all. Chest roentgenograms are similar to those in the third group, and the electrocardiogram shows right atrial and marked right ventricular hypertrophy without any evidence of hypertrophy of the left ventricle.

The venous hum is an innocent, continuous, high-pitched murmur at the supraclavicular and infraclavicular areas which sometimes may resemble the murmur of patent ductus arteriosus but can be identified readily by its obliteration following pressure on the veins in the neck and its accentuation on standing or attenuation on assuming a recumbent position. Other rare conditions with loud, continuous murmurs which may simulate the murmur of patent ductus arteriosus are ruptured aneurysm of the aortic sinus of Valsalva into the right chambers or pulmonary artery, coronary arteriovenous fistula, and aortopulmonary septal defects. In these entities the murmur usually is diffuse over the precordial area and maximal at the lower precordial area and has a more superficial quality. The murmur in aortopulmonary septal defect may occur in systole only, because of the large septal defect and the marked pulmonary hypertension. These three unusual types of arteriovenous fistula can be diagnosed definitively only by retrograde aortography. In ventricular septal defect with aortic regurgitation due to herniation of an aortic cusp into the defect, the clinical findings may simulate those of patent ductus arteriosus. The characteristic harsh pansystolic murmur and thrill

at the lower left parasternal area of ventricular septal defect and the faint, decrescendo, early diastolic blow at the base, however, differ from the crescendo systolic-decrescendo diastolic, basal, continuous murmur of patent ductus arteriosus.

### *3. Atrial Septal Defect*

Defects of the interatrial septum may be located at or just below the area of the fossa ovalis (ostium secundum) or low in the septum close to the atrioventricular ring, usually associated with splitting of the mitral or tricuspid valves (ostium primum). Occasionally the lesion may lie cephalad to the foramen ovale near the superior vena cava, and then it is almost always associated with anomalous connection of the right pulmonary veins into the right atrium or superior vena cava. The hemodynamic and clinical findings of this rare type are identical to those of the ostium secundum defects.

Ostium secundum defects comprise about 85 per cent of atrial septal defects. Clinical findings are related to the increased stroke volume of the right ventricle due to the shunt from the left atrium. The average patient is asymptomatic during childhood except possibly for slight retardation of growth in some cases with larger shunts. Characteristic clinical findings include a widely split, fixed second sound in the pulmonary area which does not vary with respiration and a soft systolic ejection murmur, usually unaccompanied by a thrill, over the same area (figure 4, atrial septal defect). If the left-to-right shunt is large, a mid-diastolic rumble may be present at or medial to the apex. Fluoroscopic and roentgenographic examination of the chest reveals mild cardiac enlargement, dilatation and increased pulsation of the pulmonary trunk and primary branches, increased pulmonary vascular markings, and absence of left atrial or left ventricular enlargement. Patients with large left-to-right shunts present, in addition, definite enlargement of the right atrium and right ventricle. The electrocardiogram reveals right axis deviation, vertical electric position and the characteristic rsR′ pattern in the right precordial tracings (figure 5a).

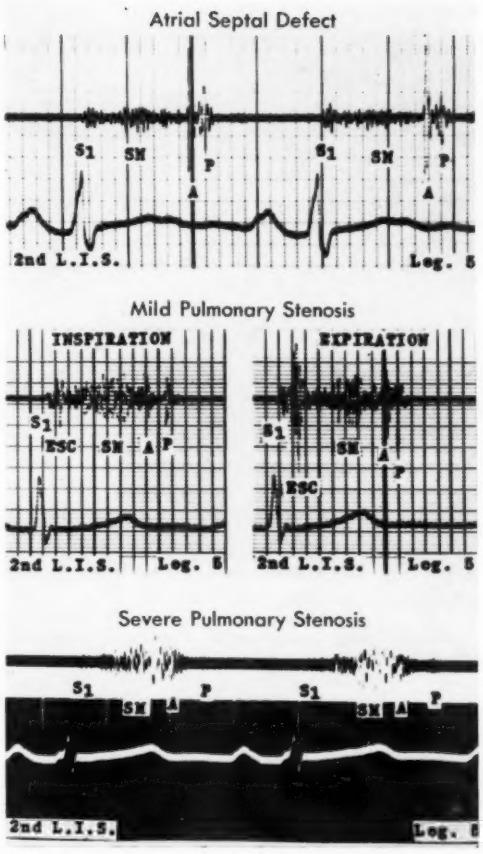



FIGURE 4. ATRIAL SEPTAL DEFECT. Phonocardiogram of nine year old girl with atrial septal defect (ostium secundum), normal pulmonary arterial pressure and a left-to-right shunt of 4 liters/minute/$M^2$. Note wide splitting of the second sound which is fixed and the systolic ejection murmur (SM).

MILD PULMONARY STENOSIS. Phonocardiogram of 10 year old girl with mild pulmonary valvular stenosis. Note ejection systolic murmur (SM), wide splitting of the second sound which becomes wider on inspiration, and the early systolic click (ESC) which is more prominent on expiration. The pulmonary component (P) of the second sound is of normal intensity.

SEVERE PULMONARY STENOSIS. Tracing of a four and one-half month old boy with severe isolated pulmonary stenosis (right ventricular pressure 121/8 mm. Hg, femoral arterial pressure 94/59 mm. Hg; pulmonary artery not entered). Note diamond-shaped murmur which goes beyond the aortic closure (A), the markedly delayed and diminished pulmonic closure (P) and absence of the early systolic click.

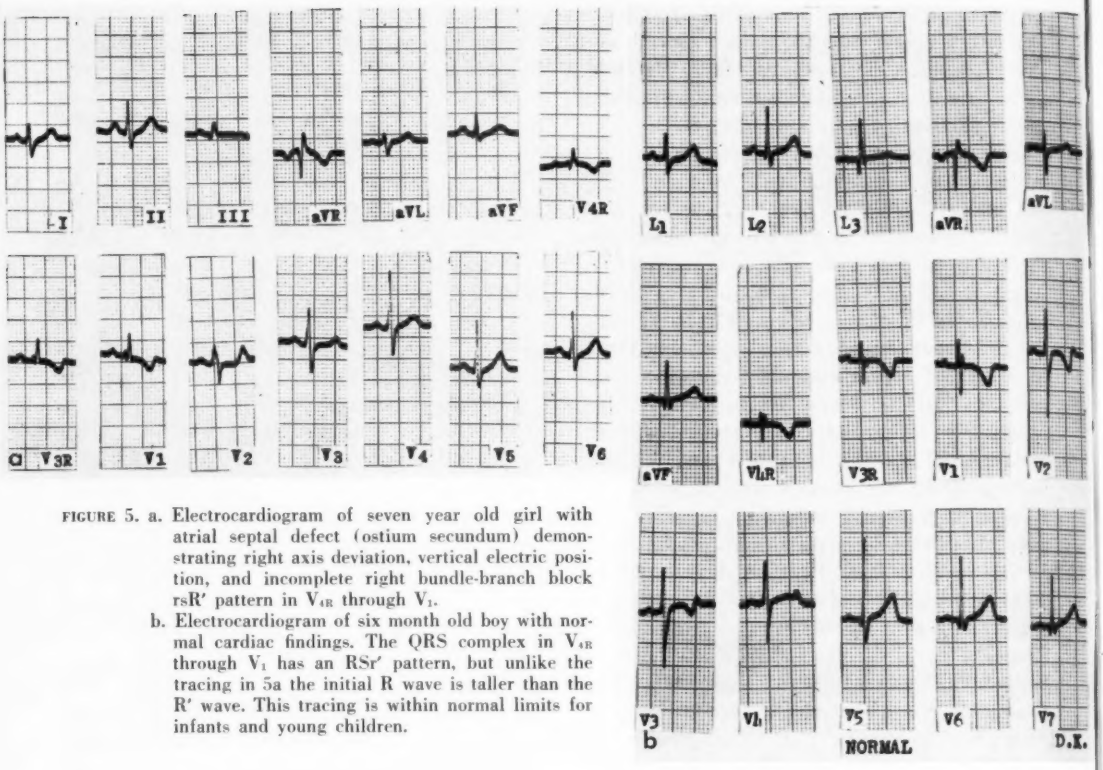



FIGURE 5. a. Electrocardiogram of seven year old girl with atrial septal defect (ostium secundum) demonstrating right axis deviation, vertical electric position, and incomplete right bundle-branch block rsR′ pattern in $V_{4R}$ through $V_1$.

b. Electrocardiogram of six month old boy with normal cardiac findings. The QRS complex in $V_{4R}$ through $V_1$ has an RSr′ pattern, but unlike the tracing in 5a the initial R wave is taller than the R′ wave. This tracing is within normal limits for infants and young children.

We have not encountered a true qR pattern in the right precordial tracings or complete right bundle-branch block in the pediatric age group.

In ostium primum defects the shunt is large, and symptoms of frequent respiratory infections, exertional dyspnea and fatigability may appear early in childhood. The heart is larger than in ostium secundum defects, and the enlargement frequently is accompanied by definite left lower parasternal lift and even a precordial bulge. The auscultatory findings described previously are also noted, and in addition a superficial, medium-frequency diastolic murmur at the tricuspid area or at the right or left lower parasternal area which, together with the ejection systolic murmur, may give the impression of a to-and-fro murmur. A blowing apical pansystolic murmur transmitted to the axilla often is present due to the associated mitral insufficiency. Chest roentgenograms are similar to those in ostium secundum defects except that the heart and pulmonary trunk are larger and left atrial enlargement may be seen. The electrocardiogram is most helpful in the diagnosis because aside from the right atrial hypertrophy and incomplete right bundle-branch block, which are also observed in ostium secundum defects, there is left axis deviation with horizontal electric position of the heart (figure 6).

Occasionally a ventricular septal defect is associated with an atrial septal defect, giving rise to a much larger left-to-right shunt and pulmonary hypertension. When the atrial septal defect is of the ostium secundum type, the atrioventricular valves are normal. When it is of the ostium primum type, the atrial and ventricular septal defects are confluent and accompanied by marked splitting of the tricuspid and mitral leaflets. This complex, known as persistent atrioventricular canal,

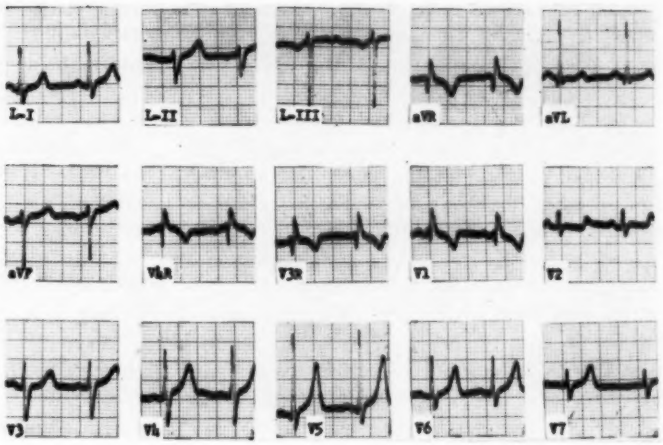



FIGURE 6. Electrocardiogram of an eight year old girl with an atrial septal defect (ostium primum) illustrating left axis deviation, horizontal electric position, and incomplete right bundle-branch block rsR′ pattern in $V_{4R}$ through $V_1$.

carries a poor prognosis; about half the patients die before the age of one year. These infants have frequent respiratory infections, dyspnea and poor growth. The heart is markedly enlarged with evidence of both left and right ventricular enlargement. The second sound is loud and closely split, and a harsh, nearly pansystolic murmur at the fourth left interspace is present, sometimes accompanied by a blowing apical systolic murmur of mitral insufficiency. As in the ostium primum defects, the chest roentgenograms reveal marked cardiomegaly involving all chambers but still predominantly the right atrium and right ventricle. The electrocardiogram similarly reveals left axis deviation, horizontal electric pattern, right atrial hypertrophy and an rsR′ pattern in the right precordial tracings with tall R′ waves.

### *4. Pulmonary Stenosis With Intact Ventricular Septum*

Isolated pulmonary stenosis is of three anatomic types: valvular, infundibular and supravalvular. The valvular type is by far the most common. The obstruction to pulmonary blood flow arising from any of these types may be mild, moderate or severe as gauged by the severity of right ventricular hypertrophy.

Patients with mild pulmonary valvular stenosis are asymptomatic. The heart size is normal. A rough, grade 3 to 4 ejection systolic murmur and thrill are present at the pulmonary area. The second sound at the pulmonary area is widely split; it varies normally with respiration, and its pulmonic component usually is of normal intensity. An early systolic ejection click usually is heard at the pulmonary area (figure 4, mild pulmonary stenosis). The chest roentgenogram is normal except for slight prominence of the pulmonary area. The electrocardiogram is normal or may show an incomplete right bundle-branch block. This entity should be differentiated from innocent or insignificant murmurs, atrial septal defect, idiopathic dilatation of the pulmonary artery, and coarctation or stenosis of the pulmonary arterial branches. The innocent or insignificant murmurs usually are not as harsh, are not accompanied by a thrill, and usually are heard best in the recumbent position. The heart sounds are normal and there is no wide splitting of the second sound, nor is there an early systolic click. In atrial septal defects the second heart sound at the pulmonary area is widely split and fixed. The murmur usually is not as loud, and early systolic clicks are uncommon, especially in children (figure 4, atrial septal defect). The pulmonary vascular markings are increased in the chest roentgenograms. Idiopathic pulmonary arterial dilatation resembles mild pulmonary stenosis in every respect except that usually it is not

accompanied by a thrill and the second sound is not widely split. In coarctation of the pulmonary arterial branches, which in our experience usually involves the right pulmonary artery, the ejection systolic murmur is not accompanied by a thrill and characteristically is transmitted widely to both lateral chest walls and the back, and an early systolic click is absent. Occasionally the chest roentgenograms show diminished pulmonary vascular markings in the affected lobe of the lung.

In moderate pulmonary valvular stenosis, also, the patients usually are asymptomatic, but they may manifest occasional exertional dyspnea with marked effort. Although the transverse diameter of the heart is not enlarged appreciably, a left lower parasternal lift is present, indicating right ventricular enlargement. A systolic ejection murmur of longer duration and a systolic thrill are present, accompanied by a wider splitting of the second sound, the pulmonic component being definitely diminished in intensity. Fluoroscopic and roentgenographic examination of the chest reveals mild to moderate cardiac enlargement with prominence of the right ventricular outflow tract in the oblique views and poststenotic dilatation of the pulmonary arteries. Pulmonary vascular markings are normal or slightly diminished. The electrocardiogram shows right ventricular hypertrophy, usually with an rsR′ pattern in the right precordial tracings.

Patients with severe pulmonary valvular stenosis are symptomatic. Fatigue and dyspnea on moderate exertion are prominent, and even syncope may occur. Heart failure may occur during infancy, accompanied by cyanosis due to a right-to-left shunt through a patent foramen ovale. Physical examination reveals marked cardiac enlargement and definite left lower parasternal lift. The stenotic systolic murmur at the base is longer than those in mild and moderate pulmonary stenosis, and it obscures the aortic closure sound at the pulmonary area. Since the pulmonary closure sound is very faint and may even be inaudible, the unusually wide splitting of the second sound (wider than in any other condition) may not be appreciated except in the phonocardiogram (figure 4, severe pulmonary stenosis). The early systolic ejection click usually is absent. Chest roentgenograms reveal marked cardiac enlargement involving the right ventricle and right atrium and diminished pulmonary vascular markings. The electrocardiogram shows right atrial hypertrophy and severe right ventricular hypertrophy of the barrage type (figure 2, lower tracing). It should be stressed that this is not an uncommon cause of progressive cardiac enlargement in early infancy; its recognition is of lifesaving importance.

Isolated infundibular stenosis is rare. It is difficult to distinguish clinically from pulmonary valvular stenosis, but the systolic thrill and murmur usually are maximal in the third and fourth left intercostal spaces, and systolic ejection clicks do not occur. Poststenotic dilatation of the pulmonary artery also is unusual. Supravalvular pulmonary stenosis is very rare. It cannot be differentiated from valvular stenosis except by selective angiocardiography.

### 5. *Aortic Stenosis*

Congenital aortic stenosis may be valvular, subvalvular or supravalvular. Recently a familial type due to muscular hypertrophy of the outflow tract of the left ventricle has been described. Valvular and subvalvular aortic stenosis are the most common types. The severity of the obstruction rather than its location determines the manifestations, and clinically the cases may be divided into mild, moderate and severe classes.

Patients with mild aortic stenosis are asymptomatic. Heart size and heart tones are within normal limits except for the frequent finding of an early systolic click at the apex and aortic area, a high-pitched sound probably produced by the thickened aortic valves as they open in systole (figure 7a). A grade 3 to 4, rough, diamond-shaped ejection systolic murmur well separated from the first and second heart sounds is present in the second right interspace and lower precordial area, well transmitted to the neck vessels. A thrill at the aortic and suprasternal areas may be present. In infants and young children the murmur may be maximal at the left lower precordial area, whereas in older children the

site of maximal intensity is the aortic area. We have not observed progression of mild aortic stenosis to severe stenosis during a 12 year period of observation of many patients with this lesion. Chest roentgenograms and electrocardiograms are within normal limits.

Patients with moderate aortic stenosis usually are asymptomatic but sometimes have dyspnea and fatigability with moderate exertion. Physical examination reveals slight cardiac enlargement with prominence of the apical impulse. An aortic systolic ejection click is not found as frequently as it is in the milder cases of aortic stenosis. The ejection systolic murmur and thrill are of the same character and distribution except that the murmur is of longer duration. Chest roentgenograms reveal mild cardiomegaly with left ventricular enlargement. Pulmonary vascular markings are normal. The electrocardiogram shows left ventricular hypertrophy, frequently with some flattening of the T waves in the left precordial tracings; the T waves are still upright. Following moderate exercise, a number of these patients may have anginal pain accompanied by flattening or even inversion of the T waves in the left precordium.

Patients with severe aortic stenosis usually are asymptomatic during childhood, although a few may manifest fatigability, exertional dyspnea, angina, syncope or, very rarely, left heart failure. Pulsus parvus et tardus with narrow pulse pressure is present. A thrill is heard in the aortic area and suprasternal notch, and the apical impulse, which is displaced to the left and downward, is unusually forceful. Auscultation reveals a long, loud, harsh, grade 4 to 5 systolic diamond-shaped murmur, maximal in the second right intercostal space parasternally and well conducted to the lower precordium and apex and to the suprasternal notch and neck vessels (figure 7b). An aortic ejection click usually is absent, and the aortic closure sound is of low intensity due to the inhibited valvular movements. The time of occurrence of the aortic closure is delayed so that it may coincide with the pulmonic closure, giving rise to a single second sound, or it may occur later than the pulmonic closure in expiration, giving rise to paradoxical splitting. Chest roentgenograms reveal left ventricular enlargement, some degree of left atrial enlargement, dilatation of the ascending aorta, and normal pulmonary vascular markings. The electrocardiogram shows severe left ventricular hypertrophy with flattened or negative T waves in the left precordial tracings.

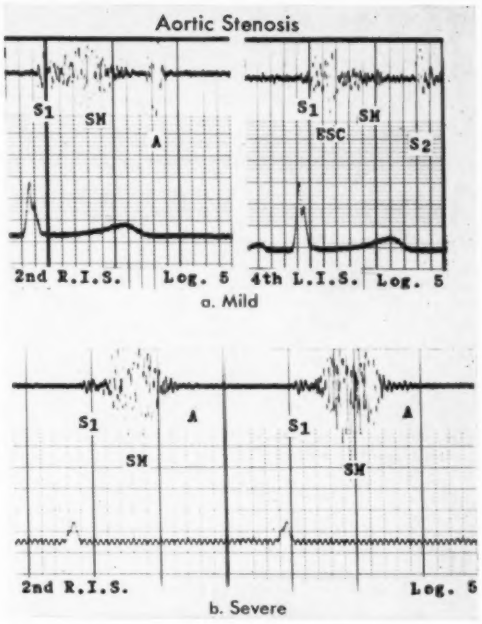



FIGURE 7. Phonocardiograms in aortic stenosis.
a. Twelve year old asymptomatic boy. Note the short diamond-shaped systolic murmur (SM), the normal intensity of the aortic closure sound (A), and the early systolic click (ESC) better heard at the fourth left interspace.
b. Seven year old boy with left ventricular pressure of 165/5 mm. Hg and aortic pressure of 85/58 mm. Hg. Note the prolonged diamond-shaped systolic murmur (SM), the very faint aortic closure sound (A) and the absence of a systolic click.

### 6. *Coarctation of the Aorta*

The clinical picture in coarctation of the aorta depends mostly on the degree and extent of aortic narrowing, location of the coarctation in relation to the aortic end of the ductus arteriosus, patency or nonpatency of the ductus arteriosus, and presence or absence

of associated intracardiac anomalies. We classify coarctation of the aorta into three groups: (1) patients with postductal ("adult type") coarctation who are asymptomatic in childhood and early adulthood, (2) patients with postductal ("adult type") coarctation who have definite symptoms and even heart failure in infancy, and (3) patients with preductal ("infantile type") coarctation.

Group 1 represents the vast majority of patients with coarctation of the aorta. Symptoms are absent in infancy and childhood and are rarely present in adolescence. The diagnosis is based on weak or absent femoral pulsations and on hypertension in the upper extremities in contrast to the hypotension in the lower extremities. When palpable, the femoral pulses may be delayed compared with the radial pulses. A soft, grade 2 to 3 ejection murmur usually is present in the interscapular region posteriorly and at times also over the second and third left interspaces anteriorly. In patients who have associated aortic stenosis the blood pressure in the arms is normal but even then the pressure in the legs is lower. Absence of symptoms in infancy and childhood is attributed to extensive, prenatally developed collateral circulation which helps prevent severe obstruction to left ventricular output. If the hypertension is severe, headaches and epistaxis may occur in older children, and if the collateral circulation to the legs is inadequate, fatigue or pain in the calves may be noted with exercise. Heart size frequently is normal.

As the child grows older, and particularly in the presence of systemic hypertension, a forceful apical impulse suggesting the presence of some left ventricular enlargement may be noted. The heart is grossly enlarged only when associated severe intracardiac anomalies are present or in exceptional cases and in later adulthood, when heart failure is present. An aortic early systolic click at the apex and at the base and an accentuated second sound are common in patients with systemic hypertension. Approximately 20 to 50 per cent of these patients have associated bicuspid aortic valves, and as they grow older and as the systemic hypertension progresses, an early diastolic blowing murmur of aortic regurgitation may be heard at the base. In the presence of associated defects (ventricular septal defect, aortic stenosis, patent ductus arteriosus) the clinical findings are dominated by those of the coexisting anomalies. Chest roentgenograms and electrocardiograms usually are normal, but in the more severe cases they may reveal evidence of left ventricular hypertrophy. Notching of the inferior margins of the third to the seventh ribs may be noted in older children, usually after the sixth or eighth year of age, although we have noted this change exceptionally in patients as young as three years of age. The notching can be seen better in the anteroposterior roentgenograms than in the posteroanterior views. Other roentgenologic findings such as elongation of the aortic knuckle and poststenotic dilatation of the first portion of the descending aorta are commonly noted after the first decade of life. In older children whose electrocardiograms reveal left ventricular hypertrophy the left precordial T waves usually are still upright, whereas in adults they usually are negative.

If the coarctation involves the left subclavian artery also, the blood pressure in the right arm is significantly (more than 15 mm. Hg) and at times considerably higher than the pressure in the left arm, and the rib notchings are noted only on the right side of the chest roentgenogram. In rare cases of anomalous origin of the right subclavian artery, arising distal to the coarctation, the pressure in the left arm is higher than it is in the right and the rib notchings are present only on the left side. A coarctation below the diaphragm may be suspected clinically by the presence of a systolic or continuous murmur in the epigastric area and notching of the lower ribs only. When the coarctation is located below the origin of the renal arteries, there usually is no associated systemic hypertension.

In group 2, patients with postductal coarctation who have definite symptoms and even heart failure in infancy, the clinical findings are similar to those in group 1 except that the heart is markedly enlarged and rales in the lower lung fields, hepatomegaly and even edema may be present. Chest roentgenograms and electrocardiograms reveal enlarge-

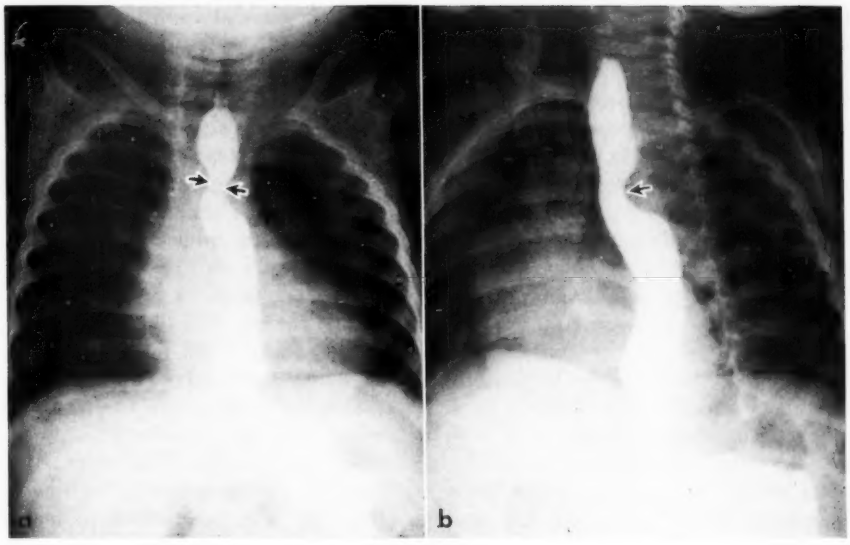



FIGURE 8. Chest roentgenograms of a one and one-half year old girl with a double aortic arch.
a. Posteroanterior view showing constriction of the barium-filled esophagus at the level of the third and fourth thoracic vertebrae (arrows).
b. Left anterior oblique view. The constriction is more marked posteriorly (arrow) because the posterior arch is much wider than the anterior one.

ment of all cardiac chambers with biventricular hypertrophy. The majority of these patients respond well to medical management; the heart size decreases and evidence of right ventricular hypertrophy gradually disappears. We have observed a number of these patients over a 5 to 10 year period, and the clinical, roentgenologic and electrocardiographic findings are then exactly as described for group 1.

In our experience, all patients with preductal coarctation (group 3) have an associated patent ductus arteriosus which usually remains patent. In contrast to postductal coarctation, where only a narrow constriction is present, in preductal coarctation there is an elongated constriction proximal to the patent ductus arteriosus. Associated ventricular septal defect is common, and at times additional serious malformations are also present such as complete transposition of the great vessels, mitral atresia, and hypoplasia of the aortic tract complex. These patients do not have adequate collateral circulation, since the ductus is distal to the coarctation and presumably no stimulus for its development during fetal life is present. Aside from the discrepant pulses and pressures of the extremities, which may not be as prominent as in postductal coarctation since the femoral pulses transmit the high pulmonary arterial pressures through the ductus, these patients have marked cardiac enlargement involving both ventricles. An early systolic click of pulmonary origin and a palpable, loud and closely split or single second sound indicate marked pulmonary hypertension. Aside from the murmur described previously, a separate, soft, grade 3 systolic murmur of maximal intensity at the left lower sternal border is common due to an associated ventricular septal defect. Chest roentgenograms reveal marked cardiomegaly with evidence of right atrial and biventricular enlargement, dilatation of the pulmonary trunk and primary and secondary branches, and normal or slightly increased pulmonary vascular markings. The electrocardiograms reveal severe right ventricular and right atrial hypertrophy and, in addition, left ventricular hypertrophy.

Differentiation of groups 2 and 3 is difficult, and a great deal of controversy exists in the literature regarding this point. We have found very useful the observation that if heart failure does develop it appears in group 3 during the first days or weeks of life, whereas in group 2 these symptoms appear in the second month or later. To us this is an outstanding practical point of differentiation between the two groups. The definitive diagnosis can be established by retrograde aortography.

### *7. Vascular Rings*

Of the various anomalies of the aortic arch, those of clinical importance because of compression of the trachea, esophagus or both are double aortic arch, right aortic arch with left ligamentum arteriosum, anomalous origin of the innominate or left carotid artery, and anomalous origin of the right subclavian artery. Although the latter appears to be the most common of the vascular rings, it has the least clinical significance because it rarely gives rise to symptoms. The most common anomaly which produces symptoms is the double aortic arch.

Vascular rings usually are isolated lesions but occasionally are associated with other major malformations such as truncus communis, tetralogy of Fallot, and tricuspid atresia. If the esophagus is compressed greatly, dysphagia and vomiting result. This may be present from birth or become apparent when the infant starts ingesting solid food. Compression of the trachea results in wheezing, stridor and chest retractions with cyanosis. Frequent respiratory infections are the major and sometimes the only clinical manifestation of this anomaly. In the absence of associated intracardiac anomalies, clinical examination reveals normal cardiac findings. Chest roentgenograms and electrocardiograms also are normal. The diagnosis is established easily by means of a barium esophogram. A persistent constriction of the esophagus at the level of the aortic arch is present which is visible in the posteroanterior view but more prominent in the lateral or oblique projection (figure 8). In the lateral or oblique view the narrowing is more marked posteriorly, and fluoroscopic examination reveals that it pulsates. This predominant forward displacement of the esophagus is due to the right or posterior aortic arch which usually is the larger of the two arches. Rarely is it necessary to instill LIPIODOL® to demonstrate the tracheal compression.

The second part of this presentation, describing the salient points in clinical diagnosis of cyanotic congenital malformations of the heart, will appear in the next issue of POSTGRADUATE MEDICINE.

# Sudden Death From Coronary Disease—the Cardiac Conundrum

LESTER ADELSON*

*Western Reserve University School of Medicine, Cleveland*

*Five hundred sudden deaths ascribed to coronary sclerotic heart disease after complete autopsy have been studied and analyzed. A broad range of morbid cardiovascular and anatomic changes was observed. Approximately one-third of the hearts showed "new" disease in the form of acute thrombotic coronary occlusion, acute myocardial infarct, or both. The remainder of the victims died suddenly of the chronic disease without the participation of any recent recognizable change in the heart. A physiologic mechanism based on differential myocardial oxygenation is postulated as the death factor in these instances. The frequent finding of an entirely normal myocardium with "fatal" coronary disease raises the issue of "hearts too good to die" and points up the advisability of instituting positive action to restore the heart beat.*

LESTER ADELSON

THAT coronary arteriosclerotic heart disease (coronary disease) can cause sudden and unexpected death is a truism requiring neither elaboration nor discussion. The forensic pathologist charged with investigating and exploring sudden and unexpected deaths can truly say that coronary disease is captain of the men of death in the twentieth-century medicolegal office.

My colleague Dr. William Hoffman and I felt that it might be worthwhile to survey the morbid cardiac-vascular anatomy of a representative large number of sudden deaths from coronary disease in order to delineate the anatomic basis (or bases) for the abrupt cessation of cardiac function. Such data might be useful in pointing the way to prophylaxis and rational therapy for these common causes of death. Accordingly we reviewed 500 consecutive sudden deaths ascribed to coronary dis-

*Pathologist and Chief Deputy Coroner, Cuyahoga County Coroner's Office; Assistant Professor of Forensic Pathology, Western Reserve University School of Medicine, Cleveland, Ohio.

Presented before the forty-fifth annual Assembly of the Interstate Postgraduate Medical Association at Pittsburgh.

TABLE 1

AGE, RACE AND SEX OF 500 PERSONS WHO DIED SUDDENLY FROM CORONARY HEART DISEASE

| AGE (YEARS) | WHITE (433; 87%) | | NONWHITE (67; 13%) | | TOTAL | |
|---|---|---|---|---|---|---|
| | *Men* | *Women* | *Men* | *Women* | *Number* | *Per cent* |
| 20-29 | 3 | 0 | 1 | 0 | 4 | 1 |
| 30-39 | 43 | 2 | 12 | 3 | 60 | 12 |
| 40-49 | 143 | 12 | 12* | 7 | 174 | 35 |
| 50-59 | 101 | 13 | 19* | 4 | 137 | 27 |
| 60-69 | 66 | 14 | 8* | 0 | 88 | 18 |
| 70-79 | 30 | 3 | 1 | 0 | 34 | 7 |
| 80-89 | 3 | 0 | 0 | 0 | 3 | |
| | 389 (78%) | 44 (9%) | 53 (10%) | 14 (3%) | 500 | |

*Includes one man of Oriental extraction.

ease after complete autopsy including histologic examination and indicated toxicologic studies.

We considered a death to be "sudden" if it occurred instantaneously or within two hours of the onset of the terminal episode. Death was charged to coronary disease when there was sufficient arteriosclerotic involvement of the coronary arteries to make the diagnosis either certain or highly probable, and when all other causes were excluded. The presence of bronchopneumonia, diabetic coma, trauma, general anesthesia and similar conditions precluded admission of a case to our study group. The only possible ancillary factor was hypertension, with or without a renal component, as indicated by cardiomegaly. Thus, we could say with a reasonable degree of certainty that all the deaths were sudden and due solely to coronary disease.

Our study is *not* representative of the total picture of coronary disease in the community as a whole or of all *fatal* coronary diseases. Rather, it reflects one facet of the over-all problem. Many instances and types of death from coronary disease are excluded. When a person who has been under the care of a physician for coronary disease dies in the hospital or at home and there are no aspects of the death requiring medicolegal intervention, either the death is not reported to the coroner's office or, if it is reported, the certification is left in the hands of the attending physician. Autopsy is not performed on all bodies brought to the coroner's office, and certification occasionally is made on the basis of history and external examination only; these instances of death ascribed to coronary disease without autopsy are also excluded from our case material.

The study material is weighted heavily in favor of the younger age groups. A coroner's autopsy is much more likely to be performed on the body of a man 45 years of age who died suddenly than on the body of an 85 year old man who died in the same fashion under the same circumstances. Occasionally, the body of an elderly person who died in this way is autopsied when anamnestic facts or environmental features indicate the advisability or necessity of postmortem examination, but generally this anatomic study under medicolegal auspices is more likely to involve the death of a younger person. Our series is also weighted unduly by deaths of persons who are not usually under regular medical care or observation (alcoholics and vagrants).

We cannot speak with any degree of certainty regarding the proportion of all deaths from coronary disease in Cuyahoga County which our series contributed during the 25 month period in which the deaths occurred. We do not know what has happened in private homes, nursing homes and hospitals with regard to fatal coronary disease, and it has been soundly established that death-certificate diagnoses, especially in the absence of complete autopsy, are misleading and unreliable.[1,2]

TABLE 2

OCCUPATIONS OF 500 VICTIMS OF SUDDEN DEATH FROM CORONARY HEART DISEASE

| CLASS | MEN (442) | WOMEN (58) | PERCENTAGE |
|---|---|---|---|
| Professional and executive | 69 | | 14 |
| Skilled mechanics | 196 | 3 | 40 |
| Semiskilled laborers | 75 | 5 | 16 |
| Unskilled laborers | 53 | 1 | 11 |
| Clerical workers | 27 | 8 | 7 |
| Housewives | | 38 | 8 |
| Unknown | 19 | 3 | 4 |
| Retired | 3 | | |

### *Some Clinical Aspects*

*Age, race and sex*—Table 1 is a breakdown of our study population by age, race and sex. The nonwhite group included three men of Oriental extraction (two Chinese and one Japanese). (Persons of Chinese and Japanese extraction comprise less than 1 per cent of the population of Cuyahoga County.) Anatomically their coronary and myocardial disease was similar to that found in Caucasians and Negroes. For the sake of simplicity we have tabulated them with the nonwhite group.

Our study population included 442 men (88 per cent) and 58 women (12 per cent). White men accounted for 78 per cent of the total, white women 9 per cent, nonwhite men 10 per cent, and nonwhite women 3 per cent. Nonwhite persons constitute approximately 20 to 22 per cent of the population of Cuyahoga County. Thus, Negroes are underrepresented in our series. Our data indicate that white men are much more vulnerable than any other racial-sexual group to a sudden fatal coronary episode.

It is significant that 12 per cent of the victims were less than 40 years of age. Coronary atherosclerosis usually is considered a disease of middle life or later, particularly in the absence of diabetes or some types of xanthomatosis. However, a diagnosis of coronary disease cannot be excluded solely because the patient is in his 20s or 30s.

*Occupation*—Our figures do not support the thesis that coronary disease chooses its victims exclusively or mainly from the executive and professional groups (table 2). Although our series included executives and professional men (doctors, lawyers, accountants), the major portion of the study population was made up of skilled mechanics (tool and die makers, machinists, etc.), semiskilled laborers (truck drivers, etc.), unskilled laborers (ditch diggers, dishwashers), clerks and housewives.

Coronary disease can and does kill suddenly in all walks of life, regardless of the manner in which the victim has earned his livelihood. No occupation confers immunity from coronary disease.

*Body habitus*—An appreciable number of reports have concerned the influence and im-

TABLE 3

RECENT CORONARY THROMBI AND ACUTE MYOCARDIAL INFARCTS IN 500 SUDDEN DEATHS FROM CORONARY HEART DISEASE

| ARTERY | RECENT THROMBUS | | ACUTE INFARCT | | ACUTE INFARCT, NO THROMBUS | |
|---|---|---|---|---|---|---|
| | *Men* | *Women* | *Men* | *Women* | *Men* | *Women* |
| Left anterior descending | 86* | 12† | 22 | 3 | 11 | 1 |
| Right coronary | 53* | 5† | 13 | 3 | 6 | 1 |
| Left circumflex | 11 | 1 | 2 | 0 | 1 | 0 |
| Number of patients | 147 | 17 | 37 | 6 | 18 | 2 |
| TOTAL | 164 | | 43 | | 20 | |

*Three instances of simultaneous thrombi in these vessels.

†One instance of simultaneous thrombi in these vessels.

TABLE 4

RECENT THROMBOTIC CORONARY OCCLUSIONS IN 500 SUDDEN DEATHS FROM CORONARY HEART DISEASE

| AGE (YEARS) | MEN | | WOMEN | | PERCENTAGE OF HEARTS WITH RECENT THROMBI |
|---|---|---|---|---|---|
| | *Recent thrombus* | *No recent thrombus* | *Recent thrombus* | *No recent thrombus* | |
| 20-29 | 2 | 2 | | | 50 |
| 30-39 | 24 | 31 | | 5 | 40 |
| 40-49 | 58 | 97 | 10 | 9 | 39 |
| 50-59 | 35 | 85 | 5 | 12 | 29 |
| 60-69 | 21 | 53 | 2 | 12 | 26 |
| 70-79 | 7 | 24 | | 3 | 21 |
| 80-89 | | 3 | | | |
| | 147 | 295 | 17 | 41 | 32.8 |

portance of body build and obesity in the development of heart disease and in deaths from this cause. Using the figures on average and ideal body weights issued recently by the Metropolitan Life Insurance Company, we found that approximately 41 per cent of the study group were overweight for their height.[3] This percentage corresponds closely with the proportion of overweight persons in the general population.[4] This correlation would tend to indicate that obesity (or overweight) is not a significant etiologic factor in predisposing to *sudden* death from coronary disease. I have been in communication with the Metropolitan Life Insurance Company about this aspect of the problem, and one of their statisticians told me that it is not merely the weight at the time of death that is important but rather the weight history.[5] Unfortunately we have no data about weight fluctuations among the persons in our study group.

### *Anatomic Observations*

While the common denominator in death and disability from coronary disease is luminal stenosis with resultant myocardial damage and dysfunction, the anatomic substrate for sudden death is extremely varied. This fact, that death can occur suddenly with such a broad variety of cardiac-vascular anatomic abnormalities ranging widely in severity, is a thought-provoking and perplexing situation.

*Recent coronary thrombi and acute myocardial infarcts* (table 3)—One hundred sixty-eight recent coronary thrombi were found in 164 hearts; four hearts each had two recent thrombi. The anatomic abnormality responsible for thrombosis, whether it is rupture of an atheromatous plaque, hemorrhage into a plaque, or luminal stenosis, usually is widespread throughout the coronary vasculature. If the hemodynamic status is such as to encourage thrombosis, there is no reason two or more thrombi cannot be laid down concurrently or in rapid succession.

Forty-three of the 164 hearts with recent coronary thrombi had an acute myocardial infarct whose histologic appearance indicated survival ranging from hours to several days following occlusion. The remainder of this group (121 persons) died so rapidly following occlusion that there was insufficient time for the development of the characteristic myocardial and cellular changes indicative of infarct.

Twenty hearts had an acute infarct without a demonstrable thrombus. This poses such questions as whether the prosector may have overlooked the clot, whether the thrombus may have been in a vessel so small that it could not be observed, and whether we were dealing with a true nonthrombotic infarct.[6,7]

Thus, 184 hearts demonstrated *acute* coronary disease, myocardial disease, or both, and 316 hearts had no recent anatomic changes present in either the coronary vasculature or the myocardium.

Recent thrombi were more frequent in the hearts of the younger victims (table 4), indicating that the younger person is more likely

TABLE 5

REMOTE MYOCARDIAL INFARCTS ("SCARS") IN 500 SUDDEN DEATHS FROM CORONARY HEART DISEASE

| AGE (YEARS) | TOTAL NUMBER OF HEARTS | | LOCATION OF SCARS | | |
|---|---|---|---|---|---|
| | *With scar* | *Without scar* | *Anterior* | *Posterior* | *Anterolateral* |
| 20-29 | 1 | 3 | 1 | 0 | 0 |
| 30-39 | 25 | 35 | 11 | 15 | 6 |
| 40-49 | 91 | 83 | 37 | 60 | 20 |
| 50-59 | 80 | 57 | 37 | 56 | 12 |
| 60-69 | 58 | 30 | 36 | 33 | 8 |
| 70-79 | 17 | 17 | 8 | 12 | 2 |
| 80 | 3 | 0 | 3 | 0 | 0 |
| | 275 | 225 | 133 | 176 | 48 |

to die with an acute thrombotic occlusion than is his older brother. This increased vulnerability may be explained by the fact that the older person may have a previously healed infarct and thus may have acquired, through the development of intercoronary anastomoses and collateral circulation, a measure of protection against the catastrophic effect of acute thrombotic coronary occlusion. Other data (see table 5) indicate that the number of healed infarcts increases progressively with the increase in age.

*Activity*—A great deal of concern revolves about what a person was doing when he had his heart attack, particularly if the fatal episode occurred while he was at work. Everybody recalls the man who died while shoveling snow, while playing handball, or when he received a telegram containing bad news. The bulk of the 500 deaths in our series occurred neither during moderate or heavy physical activity nor during an emotionally traumatic period (table 6). The distribution of recent coronary thrombi was almost uniform among the hearts of persons who had died while engaged in all types of activity and inactivity. Certainly violent physical exertion or severe emotional disturbance can create a lethal burden for a heart that is unable to meet the additional load, but from the *over-all* point of view one cannot incriminate strenuous physical activity as a common factor in sudden death from coronary disease.

*Healed infarcts*—The number of myocardial scars indicative of healed infarcts and the percentage of scarred hearts increased progressively with the ages of the victims (table 5). Microscopic areas of perivascular fibrosis were not considered pathognomonic of remote myocardial infarcts. Such foci may represent healed rheumatic or nonrheumatic myocarditis. Small zones of interstitial myocardial fibrosis can result from prolonged low-grade anoxia, a different type of lesion from the acute infarct.

There are more scars than scarred hearts because several hearts had more than one scar, indicating that many hearts can withstand severe repeated insults and still perform fairly efficiently for many years.

*Summary of anatomic changes* (table 7)—One hundred eighty-four hearts showed evidence of acute disease (coronary thrombosis, myocardial infarct, or both). Three hundred sixteen hearts had no recent demonstrable dis-

TABLE 6

ACTIVITY PRECEDING ONSET OF FATAL EPISODE IN 500 SUDDEN DEATHS FROM CORONARY HEART DISEASE

| ACTIVITY | TOTAL CASES | | CASES WITH THROMBUS | |
|---|---|---|---|---|
| | *Number* | *Per cent* | *Number* | *Per cent* |
| Sleeping | 34 | 7 | 11 | 32 |
| Resting | 68 | 14 | 18 | 26 |
| Light activity | 277 | 55 | 87 | 31 |
| Moderate activity | 95 | 19 | 38 | 40 |
| Heavy activity | 25 | 5 | 10 | 40 |
| Undetermined | 1 | | | |
| | 500 | | 164 | 33 |

TABLE 7

SUMMARY OF RECENT AND REMOTE CORONARY THROMBI AND INFARCTS IN 500 SUDDEN DEATHS FROM CORONARY HEART DISEASE

| SEX | ACUTE LESIONS (184) | | NO ACUTE LESIONS (316) | |
|---|---|---|---|---|
| | *No remote infarcts* | *Remote infarcts* | *No remote infarcts* | *Remote infarcts* |
| Men (442) | 82 | 84 (37%) | 113 | 163 (63%) |
| Women (58) | 13 | 5 (31%) | 17 | 23 (69%) |
| | 95 | 89 | 130 | 186 |

ease. One hundred thirty of the persons who had no recent or remote thrombi and a normal myocardium died suddenly of stenosing coronary vascular disease. These 130 hearts raise the issue of "hearts too good to die."[8] I will return later to a brief consideration of this group.

*Severity of coronary arteriosclerosis*—A survey was made of the degree of the arteriosclerosis in the coronary tree. The process was graded as follows: no significant disease, or reduction of lumen of slight, moderate or severe degree. The site of most severe involvement in a vessel determined the category of classification. When the process was limited to a few scattered, flat, nonocclusive plaques the artery was considered free of functional disease. If more than 75 per cent of the original lumen was present the artery was thought to be slightly involved. If the lumen was reduced to an opening ranging between one-fourth and three-fourths of its original caliber, the vessel was graded as moderately involved. If the process was more advanced, e.g., pinpoint opening, crescentic slit, remote recanalized thrombus, the process was classed as severe. The distribution of disease was noted as localized or generalized.

Table 8 reiterates what has been noted by other observers, that is, that the left anterior descending artery is most often involved by severe disease, the left circumflex artery is least often involved by severe disease, and involvement of the right coronary artery is between these two extremes. A broad range of atherosclerosis from the aspects of both severity and distribution was present in our case material. At one extreme were 11 instances of localized moderate or severe disease limited to one vessel and relatively insignificant arteriosclerosis elsewhere. At the other extreme were several hundred hearts with either severe generalized disease in all three vessels or generalized severe disease in two vessels and moderate generalized disease in the remaining artery. Between the extremes were all gradations of severity and distribution. It is noteworthy that all these people died in similar fashion despite the tremendously broad range of stenosing arteriosclerosis.

*Symptomatology*—Data referable to premonitory symptoms immediately prior to the

TABLE 8

DEGREE OF STENOSIS IN MAJOR CORONARY ARTERIES IN 500 SUDDEN DEATHS FROM CORONARY HEART DISEASE

| ARTERY | NO SIGNIFICANT STENOSIS | REDUCTION OF LUMEN | | |
|---|---|---|---|---|
| | | *25%* | *26 to 74%* | *75 to 100%* |
| Left anterior descending | 1 | 12 (2%) | 117 (23%) | 370 (74%) |
| Left circumflex | 24 (5%) | 55 (11%) | 157 (31%) | 264 (53%) |
| Right coronary | 15 (3%) | 55 (11%) | 128 (26%) | 302 (60%) |

TABLE 9

SYMPTOMS ASSOCIATED WITH FATAL EPISODE IN 500 SUDDEN DEATHS FROM CORONARY HEART DISEASE

| ANATOMIC ABNORMALITY | CASES | DEATHS WITNESSED | PRODROME | | NO PRODROME | |
|---|---|---|---|---|---|---|
| | | | *Number* | *Per cent* | *Number* | *Per cent* |
| Recent thrombus with or without infarct | 164 | 119 | 82 | 69 | 37 | 31 |
| Recent infarct, no thrombus | 20 | 9 | 7 | 78 | 2 | 22 |
| No acute lesion | 316 | 196 | 75 | 38 | 121 | 62 |
| | 500 | 324 | 164 | | 160 | |

fatal episode are recorded in table 9. These figures must be scanned with a measure of caution, because they are based on hearsay evidence. Our study was done in retrospect. The autopsy and its interpretations derive from our personal observations, but the description of the symptomatology attending the terminal episode was taken from police reports. (The police routinely investigate all sudden deaths on behalf of the coroner in Cuyahoga County.) A police officer is not a medically trained or oriented investigator, and it is probable that many reports are incomplete because of the officer's failure to ask about such symptoms or to record them. However, such errors of omission probably are present in random fashion throughout the entire series, and the figures are presented with this caveat.

Data dealing with the presence or absence of clinical symptomatology indicative of coronary catastrophe were available in 324 deaths. Death was witnessed in 128 of the 184 instances of acute coronary vascular disease, myocardial disease, or both. Eighty-nine of the victims (70 per cent) voiced or exhibited some complaint before they died, e.g., chest pain, dyspnea, nausea and vomiting, "dizziness." However, among 196 victims in whom no acute myocardial or vascular disease was found, only 38 per cent uttered or demonstrated some complaint.

If these figures have any validity, we may conclude that when sudden coronary death is precipitated by (or accompanied by) acute disease in the arterial tree or myocardium the victim is twice as likely to manifest symptomatology just before death as is the person who dies solely of coronary stenotic changes without recent thrombosis or acute infarct.

Many deaths from coronary disease are hyperacute. The victim goes from a state of apparent good health to death within a few seconds or minutes. He may die so quickly that he does not have the opportunity either to experience or to express discomfort or pain. It is also possible that the heart may be thrown into a fatal arrhythmia by factors that are insufficient to trigger cardiac pain receptors or to activate other physiologic responses and subjective complaints to myocardial anoxia.

### *Discussion*

Coronary disease is the No. 1 killer of persons in their most productive years of life. At autopsy the victims of sudden death from coronary disease present an extremely broad range of anatomic abnormalities. What are the clinical implications of this mass of postmortem anatomic data?

Several perplexing questions arise when one attempts to correlate morbid anatomy with clinical syndrome and sudden death from coronary disease. To paraphrase Winston Churchill, sudden death from coronary disease is frequently an enigma wrapped in a paradox and surrounded by a riddle. The problem is not made simpler by the well-documented observation that many persons who die from totally unrelated causes (e.g., severe trauma) often demonstrate coronary arteriosclerosis much more severe than that found at autopsy following a death ascribed to coronary disease. Coronary arteriosclerotic heart

disease presents a broad discrepancy between severity of anatomic changes, clinical symptomatology, and potential death-producing factors.

When a recent thrombus is found in a coronary artery of a person who has died suddenly, the clinician and pathologist are satisfied. The cause of death is "explained." How, then, does one "explain" a sudden death when a recent thrombus or infarct is not found in a coronary artery although there may be severe generalized stenotic disease in the coronary vasculature, and when there are no significant abnormalities elsewhere? Two-thirds of the persons in our study group did not have an acute anatomic lesion, either thrombotic or myocardial, at the time of death. (In this connection it may be noted that the diagnosis of "acute coronary occlusion" made prior to autopsy when persons with known or suspected coronary disease die suddenly is correct in only one-third of the deaths. It is probably wiser to employ the noncommittal phrase "acute coronary episode" to characterize these deaths until actual visualization of the morbid anatomic changes permits a more accurate diagnosis.) Studies similar to ours have been reported recently from the Medical Examiner's Office of the City of New York[9] and from the Medical Examiner's Office of Westchester County, New York.[10] The figures and data in each of these reports correspond quite closely with ours, indicating broad epidemiologic similarity in case material and in pathologic features.

When no recent coronary thrombus or acute myocardial disease is found in the heart of a person who died suddenly from coronary disease, what has transpired to cause death? Phrased another way, what are the death factors? A modest fraction of the persons in our study group who did not have recent disease died while engaged in strenuous physical activity. It is reasonable to postulate that they overtaxed their cardiac reserve by creating a severe discrepancy between myocardial oxygen need and ability of the coronary vessels to meet the demand. However, the majority of the victims without recent disease died while at rest, physically and emotionally, or while engaged in relatively mild activity. Here the physical and emotional stress factors are not operative.

Coronary disease can cause death by several different cardiac mechanisms: (1) increasing coronary stenosis and occlusion with progressive muscular dysfunction, damage and destruction and ultimate myocardial insufficiency; (2) sudden decrease in coronary inflow with insufficient circulation to the myocardium to maintain the heart beat; (3) a mechanism proposed by Beck,[11-14] development of an unstable electric condition in the myocardium which can initiate the onset of ventricular fibrillation. This lethal process Beck succinctly terms "self electrocution." The basis of the electric instability is differing degrees of oxygenation in various portions of the myocardium. This hypothesis is a reasonable explanation for sudden coronary death in the absence of recent vascular or myocardial disease, particularly when an intolerable physical or emotional burden has not been placed on an organ which has lost its reserve.

The next logical step is a brief consideration of the proposition of "hearts too good to die." Our data indicate that many persons who die suddenly from coronary disease have an intact myocardium. Frequently the death-producing coronary disease is a localized process with little if any stenotic disease elsewhere in the coronary tree. It is reasonable to conjecture that many such hearts could be restored to useful activity.

While many diseases wreck the machinery as they proceed to a fatal termination, coronary arteriosclerotic heart disease is an excellent example of a lethal process which stops the machinery while leaving it relatively intact. The sudden cessation of heart action in a "good" heart with coronary disease is somewhat comparable to the stoppage of a good clock when someone grasps the pendulum; the gears are good, the springs are good, and indeed the entire "works" are in excellent running order, but the clock has stopped. Should someone come along and give the pendulum a push, normal regular activity would be restored. The proof that good heart activity can be restored in many instances of sudden coro-

nary death is the increasing number of cases reported in which persons have been revived after "fatal heart attacks" by cardiac massage, electric defibrillation, or a combination of both.[15-17] Many such persons have gone on to uneventful recovery and many years of excellent cardiac function.

Today the clinician is in a position to do more than merely pronounce the patient dead when he is in attendance at such a fatality. If the doctor will accept the thesis that "this person may have a chance," he will immediately commence cardiac massage (rhythmic manual cardiac compression), electric defibrillation, or both, meanwhile insuring that the airway is patent and the oxygen supply is adequate. Proper, prompt institution of these therapeutic technics will restore life to many who previously have been given up for dead and will literally bring them back from the grave.

## REFERENCES


1. Editorial: The convenient coronary. New England J. Med. 262:149-150 (January 21) 1960.
2. Starr, I.: Heart disease as a cause of death. (Editorial.) Circulation 16:1-2 (July) 1957.
3. New weight standards for men and women. Statist. Bull. Metrop. Life Insur. Co. 40:1-4 (November-December) 1959.
4. Frequency of overweight and underweight. Statist. Bull. Metrop. Life Insur. Co. 41:4-7 (January) 1960.
5. Marks, H. H.: Personal communication.
6. Foord, A. G.: Embolism and thrombosis in coronary heart disease. J.A.M.A. 138:1009-1012 (December 4) 1948.
7. Feiks, K. F.: Pathogenesis of myocardial infarct. Wien. Ztschr. inn. Med. 40:345-355 (September) 1959.
8. Beck, C. S. and Leighninger, D. S.: Should patients with coronary heart disease be treated by surgical operation? Ohio M. J. 56:809-815 (June) 1960.
9. Weinberg, S. B. and Helpern, M.: Circumstances related to sudden and unexpected death in coronary disease. In Rosenbaum, F. F. and Belknap, E. L. (Editors): Work and the Heart. New York, Paul B. Hoeber, Inc., 1959, chap. 33, pp. 288-292.
10. Spain, D. M. and Bradess, V. A.: Relation of sex, age and physical activity to sudden death from coronary arterial occlusion. *Ibid.*,[9] chap. 32, pp. 283-287.
11. Beck, C. S.: Coronary heart disease—three dominant causes of death. Am. J. Surg. 95:743-751 (May) 1958.
12. ——: Coronary heart disease—an evaluation and criticism of present day concepts. (Editorial.) Am. J. Cardiol. 1:547-552 (May) 1958.
13. ——: Coronary heart disease after twenty-five years. J. Thoracic Surg. 36:329-345 (September) 1958.
14. ——: Coronary artery disease—a report to William Harvey 300 years later. Am. J. Cardiol. 1:38-45 (January) 1958.
15. Beck, C. S., Weckesser, E. C. and Barry, F. M.: Fatal heart attack and successful defibrillation. J.A.M.A. 161:434-436 (June 2) 1956.
16. Zoll, P. M., Linenthal, A. J. and Zarsky, L. R. N.: Ventricular fibrillation; treatment and prevention by external electric currents. New England J. Med. 262:105-112 (January 21) 1960.
17. Nast, P. R., Pennypacker, C. S. and Wagner, J. A.: Successful external electrical defibrillation in acute myocardial infarction. Circulation 22:138-143 (July) 1960.

# Self-help Devices:

## Homemaking: Dishwashing

EDWARD W. LOWMAN AND HOWARD A. RUSK

Institute of Physical Medicine and Rehabilitation
and the Arthritis Self-help Device Office*

*New York University Medical Center, New York*

SINCE conservation of energy is an important factor in managing a disease or disability, ambulatory homemakers should orient themselves to doing as many tasks from a sitting position as possible. Dishwashing is particularly suited to sit-down work, whether the patient sits in a wheel chair or on a stool or standard kitchen chair.

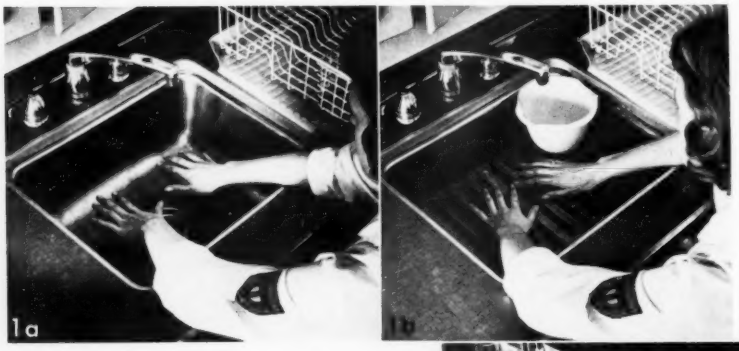



FIGURE 1. To establish a good working height at the sink for standing or sitting, place the palms of the hands in the bottom of the sink bowl without leaning forward (a). If the sink is too deep, a rack can be improvised to hold a dishpan at the needed height (b).

FIGURE 2. For the homemaker to function efficiently, the work area must be well organized to permit a coordinated flow of activity from right to left or vice versa without backtracking.

FIGURE 3. Dishes should be air-dried to conserve energy. The best results are obtained by using either liquid or powder detergents which rinse off completely. Cleaning aids should be within comfortable reach at all times. Soak the soiled pots and pans during the meal, and the soiled dishes immediately after they have been used.

*Supported at the Institute by the Arthritis and Rheumatism Foundation.

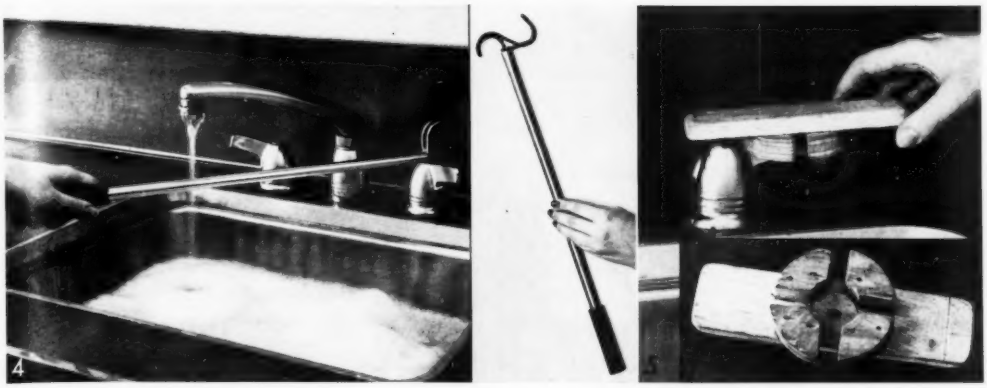


FIGURE 4. If reaching the faucet is difficult, a simple solution is to screw a closet hook into a dowel of the needed length and use it to open and close the faucet.

FIGURE 5. If inadequate grasp is a problem, a wooden piece made to fit over the faucet will give better leverage.

## For Those Who Must Function Singlehandedly

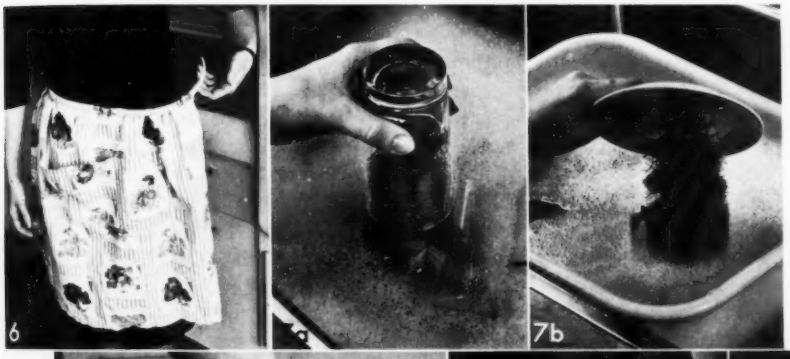


FIGURE 6. A hooped apron is much easier to put on and remove than an apron with ties.

FIGURE 7. A suction-based brush for washing glasses (a) can also help to remove stubborn spots on dishes (b).

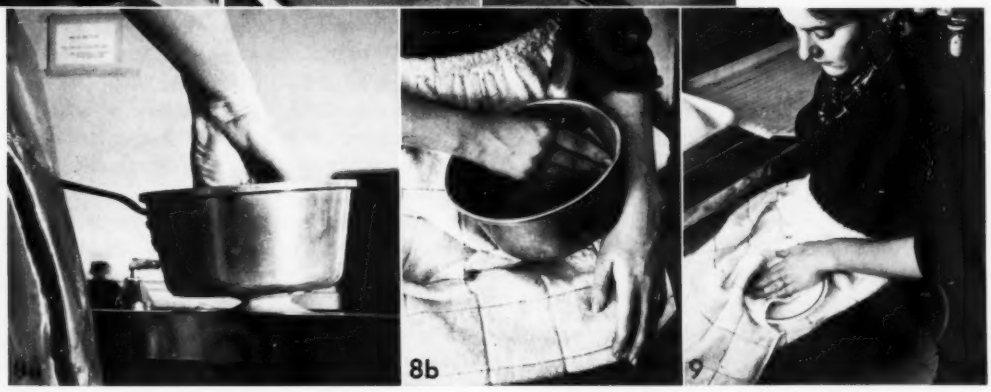


FIGURE 8. To stabilize pots and pans for scouring, a double-suctioned base clinging both to the counter and to the container can be used (a), or some traction can be created by putting a damp cloth underneath the pot. Another approach is to hook the handle of the pan under the nonworking arm (b).

FIGURE 9. Although we recommend that dishes be air-dried, they can be dried manually with only one hand by putting the item on a towel placed on the lap and wiping it with part of the towel. The therapist demonstrating this is actually wearing a terry-cloth hooped apron and is drying the dish with part of the apron.

# Management of Acute Renal Failure

W. A. KREHL*

*Marquette University School of Medicine, Milwaukee*

## *Introduction*

W. A. KREHL

FEW situations in medicine call for as aggressive and intelligent application of clinical knowledge, judgment and physiologic principles as does the management of acute renal failure.[1] In lower nephron nephrosis with acute renal failure, the chief pathologic condition is found in the tubules. The kidneys grossly are swollen and edematous. On microscopic examination, only insignificant changes are seen in the glomeruli, while major lesions, consisting of necrosis of the epithelial cells, are evident in the tubules. Although any part of the tubule may be damaged, the lower segments are usually most severely altered.[2] In addition, casts are usually found in the terminal segments of the tubules. These vary to some extent, depending on the nature of the noxious agent or factor that caused the acute renal failure. The exact significance of these casts is not known.

Since the tubular lesions are confined to epithelial cells, they are potentially reparable. Evidence of epithelial cell regeneration may be seen as early as the fourth or fifth day; usually, after 12 to 14 days, the tubular epithelium may be restored, but function is impaired in rate and manner. Clinical management is therefore directed at maintaining the patient in the best-possible physiologic status while nature carries on its repair. The phases of oliguria, diuresis and convalescence each demand individualized care and a shifting focus of attention.[3]

Proper management of acute renal failure is predicated, of course, on an early and correct diagnosis. Thereafter, every attention must be provided to avoid major complications, which include overhydration, electrolyte imbalance and excessive accumulation of the products of protein catabolism and serum potassium. Infection, a major cause of death, must be avoided or, if present, appropriately treated. Bleeding tendencies associated with uremia and acute renal failure must be watched for and treated promptly. Circulatory failure, congestive heart failure and pulmonary edema must be guarded against, and digitalization must be instituted early. Finally, the decision concerning the use of hemodialysis or peritoneal dialysis must be made at the proper time. The following discussion is a consideration of

*Associate Professor of Medicine, Marquette University School of Medicine, Milwaukee, Wisconsin.

these problems, which also have been reviewed elsewhere.[4-6]

### *Diagnosis*

Haste or carelessness in diagnosing acute renal failure may lead to disaster. A good history, careful physical examination, examination of the urine and its sediment, and determinations of serum electrolytes and blood urea nitrogen (BUN) are prerequisites to a good diagnostic evaluation.

### *Is Oliguria Due to Dehydration or Electrolyte Imbalance?*

Since treatment of renal failure hinges largely on the restriction of fluid intake and avoidance of excess electrolytes, the importance of this issue is obvious. A careful review of the circumstances preceding oliguria, with particular attention to routes of fluid loss (vomiting, diarrhea, sweating, fever, hyperpnea, intestinal or biliary drainage, paracentesis, etc.) and to the quantity and nature of fluids supplied, is of utmost importance. Physical findings of dehydration, such as loss of skin turgor, while important, may be absent if fluid losses are acute. The finding of a concentrated urine with a high osmolarity and high urea content, increased hematocrit, increased serum protein levels, or increased serum sodium in excess of 150 mEq. per liter is adjunctive information which may be helpful in dehydration. High or elevated BUN may be seen in dehydration as well as in acute or chronic renal failure. Obviously, such factors as prerenal filtration rate may influence urine osmolarity, and pre-existing anemia, hypoproteinemia, hyponatremia, etc., may obscure the previously mentioned signs of dehydration.[4]

Frequently, in the absence of a convincing history, the sum of these data does not adequately exclude dehydration, particularly since vomiting is often an integral part of early renal insufficiency. In this circumstance, it is of value to give intravenously and rapidly 1 liter of 5 per cent glucose (or 0.9 per cent saline if findings indicate) and to watch carefully for increased urinary output or decreased urine concentration. If one or both of these occur, it is usually safe to proceed with giving appropriate intravenously administered fluids, with the expectation that dehydration will be corrected and urinary output resumed.

### *Reversible Renal Failure*

Few circumstances are more tragic than the failure to recognize causes of chronic renal failure which are reversible in their early stages but which, if undiagnosed and not treated, lead to progressive, chronic and irreversible renal damage. These common reversible causes of chronic renal failure are obstructive uropathy as the result of calculi in the urinary tract, prostatic hypertrophy, urethral stricture, or periureteric fibrosis; infection, such as superimposed acute pyelonephritis; and metabolic states, such as deficiency of potassium, hypercalcemia or sodium depletion.[7] Hypercalcemia may be associated with vitamin D toxicity, hyperparathyroidism, milk-drinker's syndrome, or sarcoidosis.

### *Is Obstruction Present?*

Bladder neck obstruction is a common finding, and more than one case of "acute renal failure" has been cured by the palpation of a greatly distended bladder and passage of a urethral catheter or even replacement of a plugged catheter already in place. Although less common, bilateral ureteral obstruction can occur as a result of a pelvic mass (hemorrhage or tumor), surgical injury or bilateral calculi. When doubt exists, the demonstration of anatomic patency by the passage of ureteral catheters to the renal pelvis is most helpful. Total anuria is not characteristic of acute renal failure and should immediately suggest obstructive uropathy.[7]

### *Is Oliguria the End Stage of Chronic Renal Disease?*

In an oliguric, uremic, acidotic patient without antecedent history, it is most difficult to decide whether or not chronic renal disease is present. In this situation, carefully directed medical management, possibly with the aid of a well-timed hemodialysis and renal biopsy, may be most valuable if sufficient clinical improvement can be obtained. If sudden oliguria occurs in a previously well-compensated case

of chronic renal disease and if a specific cause can be indicated to suggest acute renal failure with tubular epithelial necrosis, hemodialysis may enable the patient to recover his previous state of renal function and may prolong life. A different consideration must be given in the end stages of a chronic, relentlessly progressive renal disease. Here, hemodialysis seems out of place and may hasten death.

### *Acute Renal Failure*

Diagnosis of acute renal failure may be difficult. As indicated previously, oliguria, elevated BUN, and changes in urine osmolarity and specific gravity may not suffice. The clinical background or history is important. Oliguria following trauma, obstetric accidents (particularly criminal abortions), ingestion of known nephrotoxic agents, shock associated with major surgery or resulting from other causes, severe body burns, or transfusion reactions resulting from mismatched blood must raise a strong suspicion of acute renal failure with tubular necrosis.

Again, a careful study of the urine is helpful in diagnosing acute renal failure. As a general rule (but not invariably), the osmolarity of the small volume of urine approaches that of plasma. Urinary urea is low while blood urea is elevated, and sodium is present in the urine in an appreciable concentration (40 to 90 mEq. per liter). While low urine urea and high urinary sodium are indicative of acute renal failure, high urine osmolarity and high urine concentration are evidence of good renal tubular function. Low urine osmolarity and low sodium concentration are not necessarily diagnostic of either situation.[8-10]

### *Principles of Management*

Four major problems face the patient as a direct consequence of acute renal failure: (1) No route is available for the excretion of the end products of protein catabolism; (2) nonvolatile acids cannot be excreted; (3) renal regulation of water balance is lost; and (4) potassium excretion is no longer possible. These lead to additional clinical complications. The development of uremia results in lethargy and gradual loss of responsiveness, which in turn favors the development of atelectasis and pneumonia. Uremia causes nausea, vomiting, increased distention and increased tendency toward bleeding from the gastrointestinal tract. Thrombopenia, as well as anemia, often is seen. Excessive accumulation of fluids and tachycardia which is associated with sepsis and fever increasingly strain the heart, leading to congestive heart failure, pulmonary edema and death. Cardiac arrhythmias and cardiac arrest are not uncommon, and may relate to severe elevations of serum potassium.

### *Managing the Catabolic Response*

Since nitrogenous wastes, hydrogen ions and potassium ions are derived largely from protein, the elimination of protein from oral and intravenous feedings seems obvious. Of equal importance is reduction of the patient's catabolism of his own protein stores to a minimum. This is best done by providing an adequate intake of nonprotein calories. The use of at least 100 gm. carbohydrate per day is needed to prevent ketosis and minimize protein breakdown. Unfortunately, the stress imposed by trauma, tissue necrosis, infection and fever produces continued protein catabolism despite the administration of adequate calories. In these circumstances, very rapid increases in serum BUN and potassium lead to rapid deterioration and death unless treated by hemodialysis.

Testosterone (25 to 50 mg. per day intramuscularly)[11] or norethandrolone (10 to 20 mg. per day)[12] may help to minimize protein metabolism in the absence of stress, but these agents are not significantly effective otherwise. When acceptable, without causing nausea and vomiting, nutrients should be given by the oral route. Hard candy, syrup, ginger ale and other forms of pure carbohydrate are quite satisfactory. They help stimulate salivary flow and reduce dryness and cracking of the oral mucosa.

When intravenously administered fluids are needed, a catheter threaded through an arm vein into the superior vena cava provides the safest route for continuous use.[1] Such a well-placed catheter can also serve should the pa-

tient require hemodialysis. Because total fluid intake is restricted to small volumes, concentrated carbohydrate solutions from 10 to 40 per cent may be used to provide needed calories. Ethanol (95 per cent, up to 100 cc. daily) may be added to the intravenously given fluids, and this adds materially to the caloric intake.[5] Ethanol should not be used in patients with concomitant liver disease. Vitamin B complex in at least maintenance (preferably therapeutic) amounts should be provided every day.

Devitalized tissue must be debrided promptly, and accumulations of blood and infection by-products drained.[13] This makes the management of acute renal failure in conditions of trauma, burns and surgery much more complicated, but failure to debride and drain will lead to disproportionate elevations of nitrogenous end products, serum potassium and phosphate.

Excessive elevations of serum potassium must be avoided. This can best be done by measures which favor retention of potassium in the cell: (1) the administration of 10 to 20 units of regular insulin in the intravenously administered fluids containing carbohydrate and (2) the prevention of metabolic acidosis by administering sodium lactate or sodium bicarbonate if the serum carbon dioxide level falls significantly. As much as 200 ml. of molar sodium lactate may be given intravenously over a three hour period to lower plasma potassium rapidly.[14] Cation exchange resins in the sodium cycle have proved effective in treating potassium intoxication.[15] They may be given as oral mixtures alone or, preferably, with sorbitol to promote gastrointestinal emptying, or they may be used as enemas.[4] Both methods are effective.

One must avoid the use of fruit juice and other potassium-containing foods or drugs. A common error is the use of potassium penicillin in the treatment of infections in acute renal failure. The sodium salt of penicillin should be used if this antibiotic is needed.

### *Fluid Control*

All fluid intake and output should be very accurately recorded, and the patient must be weighed daily. The necessary fluid intake each day can be calculated on the basis of 0.5 to 0.6 ml. per kilogram of body weight per hour, plus the volume of fluid lost in urine, vomitus or feces or in drainage from gastric tube, fistulas, etc. Water of oxidation represents about 300 ml. per day and should be deducted from intake. The best guide to proper fluid intake may be obtained from the daily weight loss, which should approximate from 0.2 to 0.4 kg. for the average patient in acute renal failure. For most patients, 400 ml. of fluids per day, plus the amount excreted as urine, plus gastrointestinal losses is adequate to maintain proper fluid balance.

It is best not to use indwelling catheters in order to avoid occurrence of urinary tract infection that they induce. The patient should void if at all possible. If the patient does not void every 24 hours, direct catheterization is done with very careful aseptic technic.

### *Infection*

It has been reported that infection causes 45 per cent of deaths in military post-traumatic renal insufficiency.[16] Infection is also the chief cause of death in civilian cases of acute renal failure.[17] To overcome this serious complication, every effort must be made to provide strict environmental asepsis. Isolation technic, positive-pressure ventilation to avoid atelectasis, the use of skin germicides, prevention of bed sores and ulcers, and avoidance of indwelling catheters are all important factors in preventing infection. Prophylactic use of antibiotics must be avoided. Culture and sensitivity studies of bacterial infections will indicate the appropriate antibiotic therapy. In renal failure with oliguria, the half-life of penicillin, erythromycin, chlortetracycline and chloramphenicol is about the same as in the normal condition, and they are therefore the drugs of choice.[18]

### *Congestive Heart Failure*

Overhydration, sepsis and fever with tachycardia, anemia, and uremia with acidosis and hyperventilation tend to increase the work of the heart and favor the development of congestive heart failure. For this reason, digitali-

zation may be required. Since the oliguric patient may have elevated serum potassium levels, digitalis is usually well tolerated; however, overuse of the drug must be avoided, since its renal excretion is negligible during the oliguric phase. DIGOXIN® at this time is the drug of choice, since the hazard of toxicity is reduced.

### *Bleeding Tendencies*

Uremic patients are anemic and tend to have increased erythrocyte destruction and impaired erythropoiesis.[19] Furthermore, bleeding from the intestinal tract is a frequent complication in uremia. This is a serious contribution to the elevation of the BUN and serum potassium. It has also been shown that there are platelet defects in uremic patients with thrombopenia.[20] The use of fresh plasma or platelet transfusions may therefore be of value in managing hemorrhage in the uremic patient.

### *The Diuretic Phase*

The oliguric stage usually lasts from 12 to 14 days. The onset of the diuretic phase is heralded by a daily increase of 50 to 100 per cent in urine volume over each preceding day. While this usually evokes enthusiasm and optimism, the chemical findings may be most discouraging, for the BUN may continue to rise or plateau for several days after the onset of diuresis. Hemodialysis may become necessary in this early diuretic stage. As soon as the daily urine volume exceeds 400 ml., it usually increases steadily at a rate of 250 to 300 ml. per day. Thereafter, the mean daily urine volume is stabilized at 2000 to 2500 ml. per day. The degree of hydration and the adequacy of electrolyte balance at the onset of the diuretic phase will be most important in establishing the amount of sodium, potassium and water needed for replacement. Hyponatremia and hypopotassemia may develop with great rapidity. Slight dehydration may impair the renal clearance of nitrogenous waste products. If overhydration is not present at the onset of diuresis, urinary losses do not usually become excessive. At any rate, fluid intake should usually not exceed 3000 ml. per day, and this should contain adequate electrolytes to replace losses. The ability to reabsorb sodium returns early, and prolonged salt wasting is not common beyond 7 to 10 days. It may be prolonged by the overuse of salt and water.

### *Convalescence*

By the time the diuretic stage has passed, a long period of illness has been endured, lasting an average of five weeks. Since protein intake has been virtually zero, endogenous body protein breakdown may be as much as 1.5 kg., about an eighth of the total body content.[3] Therefore, the diet should provide an abundant level of protein, and it should be adequate in calories so that protein is not used for caloric purposes. Gradual return to activity is needed, since muscular weakness and reduced muscle mass are significant. Vitamin intake should be higher than maintenance levels.

### *Hemodialysis*

Hemodialysis has been used more and more in the treatment of acute renal failure.[21,22] It should be emphasized that this procedure requires more than casual experience and is best done in larger referral centers where a competent team is available to apply this technic. The Kolff twin-coil kidney is a most adequate device for hemodialysis and has the added advantage of ultrafiltering water.[23] Many types of artificial kidneys have been used.[24]

There is no completely uniform set of indications for instituting hemodialysis. Actually, the clinical condition of the patient as judged by experience is the best general guide. Usually, however, hemodialysis is justified when any one of the following is present: (1) serum potassium levels above 7.5 mEq. per liter, despite therapy with cation exchange resins; (2) BUN above 350 mg. per cent; (3) electrocardiographic evidence of intraventricular block with widening of the QRS complexes from hyperkalemia; (4) uremic stupor, coma or increasing central nervous system irritability; or (5) blood bicarbonate below 10 mEq. per liter. Excessive edema also may be relieved by hemodialysis, which may prevent the development of pulmonary edema.

Contraindications to hemodialysis are few

and, if hyperkalemia threatens life, this procedure may be resorted to in spite of contraindications, since some may be correctable. In most patients, severe hypotension, myocardial infarction or bleeding, especially central nervous system bleeding, precludes the use of hemodialysis. Regional heparinization may eliminate the bleeding contraindication. If respiratory failure is present, it is treated concomitantly by tracheal intubation and assisted breathing. Shock, if present, may improve as hemodialysis proceeds, and may be treated with vasopressors. Renal failure from chronic renal disease, while not a contraindication to hemodialysis, is not benefited and is associated with a high mortality rate. Again, it should be emphasized that clinical judgment based on experience is the best guide to follow in the use of hemodialysis. In general, early hemodialysis is employed more commonly, and, in some centers, it has been used daily as a prophylactic measure in treating acute renal failure.[25] This permits an unrestricted dietary intake, favors better wound healing, prevents wasting, and provides a better defense against infection.

It is most difficult to evaluate the effects of hemodialysis as a lifesaving procedure. Mortality statistics indicate a fairly constant level of about 50 per cent in the various centers.[26] Trauma, burns, old age and sepsis are associated with a higher incidence of death.

### *Peritoneal Dialysis*

Hemodialysis is best done in active centers where it is frequently performed. Peritoneal dialysis, however, can be readily done in any hospital. Prepared electrolyte solutions, with special catheters and a closed system of infusion and drainage, are available commercially. This procedure now has largely eliminated such complications as peritonitis, overhydration, electrolyte abnormalities, leakage and drainage difficulties. Although not as efficient as hemodialysis, peritoneal dialysis can be repeated daily.[27]

### *An Ounce of Prevention*

It is, of course, more desirable to prevent disease than to have to treat it. The economics alone make it obvious that acute renal failure is to be avoided. The overzealous use of blood transfusions, with the inherent chance of mismatch, should be eliminated. There is virtually no real indication for the hundreds of one unit blood transfusions that are so common in our hospitals.

Noxious substances may damage the tubules and escape reabsorption. They are therefore concentrated in their progress through the tubules. It is evident, therefore, that measures which reduce the reabsorption of water and consequently the concentration of nephrotoxic agents should reduce the chance of tubular injury. Adequate fluid intake, ensuring a large flow of urine, can minimize the incidence and severity of lower nephron nephrosis.

Furthermore, more adequate hydration of patients prior to surgery can help minimize the threat of shock, reduced renal blood flow, and renal ischemia leading to tubular damage with acute renal failure. Greater care should be exercised to keep nephrotoxic chemicals and medicines out of the hands of children.

### *Comment*

Acute renal failure must not be handled with panic or masterful inactivity; it must be approached with a vigorous and intelligent application of sound physiologic principles. Hemodialysis may be a lifesaving procedure, but must not replace sound medical care. Hemodialysis is best applied in those centers in which an experienced team is available.

## REFERENCES


1. Merrill, J. P.: The Treatment of Renal Failure. New York and London, Grune & Stratton, Inc., 1955, p. 238.
2. Lucke, B.: Lower nephron nephrosis. Mil. Surgeon 99:371-396, 1946.
3. Loughridge, L. W., Milne, M. D., Shackman, R. and Wootton, I. D. P.: Clinical course of uncomplicated acute tubular necrosis. Lancet 1:351-355 (February 13) 1960.
4. Franklin, S. S. and Merrill, J. P.: Acute renal failure. New England J. Med. 262:711-718, 1960.
5. Schulz, E. G. and Murphy, F. D.: Treatment of acute renal failure. A.M.A. Arch. Int. Med. 103: 453-459, 1959.
6. Kiley, J. E., Powers, S. R., Jr. and Beebe, R. T.: Acute renal failure. *Ibid.*,[4] pp. 481-486.
7. Brun, C., Hilden, T., Iverson, P. and Raaschou,

F.: Diseases of the kidney. Ann. Rev. Med. 7:245-262, 1956.
8. Bull, G. M., Joekes, A. M. and Lowe, K. G.: Renal function studies in acute tubular necrosis. Clin. Sc. 9:379-404, 1950.
9. Meroney, W. H. and Rubini, M. E.: Kidney function during acute tubular necrosis: Clinical studies and theory. Metabolism 8:1-15, 1959.
10. Waugh, W. H.: Functional types of acute renal failure and their early diagnosis. *Ibid.*,[5] pp. 686-689.
11. Freedman, P. and Spencer, A. G.: Testosterone propionate in treatment of renal failure. Clin. Sc. 16:11-22, 1957.
12. McCracken, B. H. and Parsons, F. M.: Use of Nilevar to suppress protein catabolism in acute renal failure. Lancet 2:885, 1958.
13. Meroney, W. H. and Herndon, R. J., Jr.: Management of acute renal insufficiency. J.A.M.A. 155:877-883, 1954.
14. Black, D. A. K.: The treatment of renal disease. Brit. M. J. 1:667-671, 1960.
15. Elkinton, J. R., Clark, J. K., Squires, R. D., Bluemle, L. W., Jr. and Crosley, A. P.: Treatment of potassium retention in anuria with cation exchange resin; preliminary report. Am. J. M. Sc. 220:547, 1950.
16. Balch, H. H., Meroney, W. H. and Saks, Y.: Observations on surgical care of patients with post-traumatic renal insufficiency. Surg. Gynec. & Obst. 100:439-452, 1955.
17. Parsons, F. M. and McCracken, B. H.: Artificial kidney. Brit. M. J. 1:740-751, 1959.
18. Kunin, C. M. et al.: Persistence of antibiotics in blood of patients with acute renal failure. J. Clin. Invest. 38:1509, 1959.
19. Erslev, A. J.: Erythropoietic function in uremic rabbits. A.M.A. Arch. Int. Med. 101:407-417, 1958.
20. Rath, C. E., Mailliard, J. A. and Schreiner, G. E.: Bleeding tendency in uremia. New England J. Med. 257:808-811, 1957.
21. Merrill, J. P.: The artificial kidney. Arch. Int. Med. 106:195-200 (July) 1960.
22. Goldsmith, H. J., Nakamoto, S. and Kolff, W. J.: Expanding the indications for treatment with the artificial kidney. Lancet 2:111-114, 1960.
23. Kolff, W. J. and Watschinger, B.: Further development of the coil kidney: Disposable artificial kidney. J. Lab. & Clin. Med. 47:969-977, 1956.
24. Kolff, W. J. and Higgins, C. C.: Dialysis in treatment of uremia: Artificial kidney and peritoneal lavage. Tr. Am. A. Genito-Urin. Surgeons 45:110-135, 1953.
25. Teschan, P. E., O'Brien, T. F. and Baxter, C. R.: Prophylactic daily hemodialysis in the treatment of acute renal failure. Surg. Forum 10:362, 1960.
26. Teschan, P. E. and Mason, A. D., Jr.: Reversible renal failure in rats: Experimental tool. Clin. Res. 6:294, 1958.
27. Maxwell, M. D., Rockney, R. E. and Kleeman, C. R.: Peritoneal dialysis. I. Techniques and applications. J.A.M.A. 170:917-924, 1959.

1961

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 13-16 Statler Hilton Cleveland, Ohio

L. REED CRANMER, M.D.

Toledo, Ohio

Keep Listening

With the more accurate and extensive knowledge of the anatomy and physiology of the ear and the improved technologic armamentarium for examination, diagnosis and treatment of ear diseases, treatment for conserving and restoring hearing has become more successful than ever before. Advances in this field and their practical application in considering the more common otologic diseases causing deafness will be reviewed. Recent advances in microsurgery of the ear will be described briefly.

**Complete program available by writing to Dr. E. R. Schmidt, Program Chairman, Box 1109, Madison 1, Wisconsin.**

*SCIENTIFIC EXHIBIT*

# CANCER

# Prevention of Dissemination

WILLIAM J. GROVE, STUART S. ROBERTS, LEROY LONG, OLGA M. JONASSON AND WARREN H. COLE

*Department of Surgery*
*University of Illinois College of Medicine*
*Research and Educational Hospitals*
*Chicago*

## INTRODUCTION

At the present time, more than one-half of the patients having curative resections for cancer return with metastases and die.[1] Undoubtedly, microscopic metastases were already present in some of these patients at the time of treatment. We are of the opinion, however, that in many patients certain phases of the initial management contribute to the dissemination of cancer.

Review of the mechanisms of dissemination indicates that certain preventive measures can be taken to minimize recurrences and metastases.

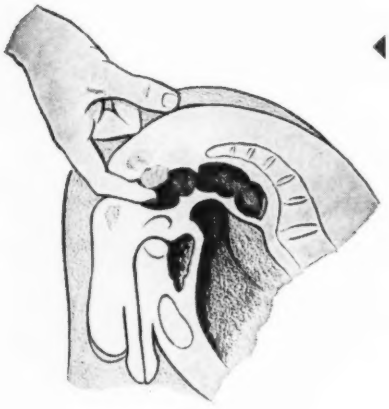
Adapted from an exhibit shown at the American College of Surgeons Clinical Congress in San Francisco, California.

# CLINICAL PROCEDURES
## That May Disseminate Cancer

## Physical Examination

Manipulation during pelvic or rectal examination and palpation of solid tumors have been associated with showers of cancer cells in the blood stream during:

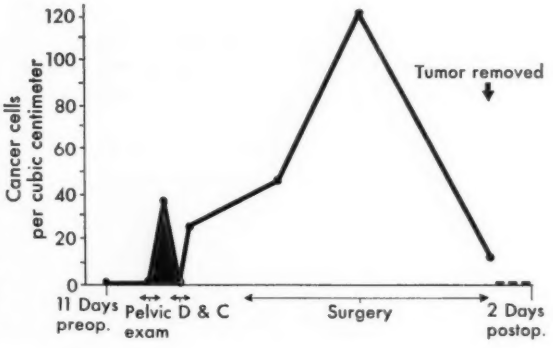
Rectal examination[2]
Palpation of an abdominal mass[3]
Pelvic examination[4]
Rupture of malignant ovarian cyst during pelvic examination[4]



◀ Rectal examination.

Palpation of abdominal mass. ▶

◀ Pelvic examination.

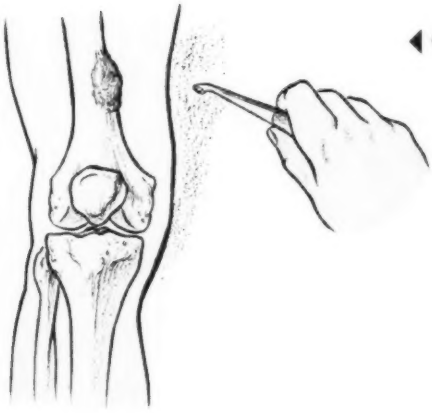



Cancer cells in the peripheral blood (antecubital vein) during resection of ovarian carcinoma. ▶

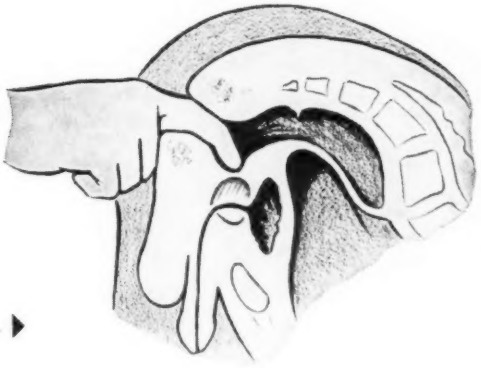
## Diagnostic Procedures

Massage to obtain secretions or the opening of vascular channels during biopsy has been associated with showers of cancer cells in the blood stream during:

Curettage of malignant bone tumor[5]
Prostatic massage[6]
Uterine curettage[7]
Curettage of uterine adenoacanthoma[7]

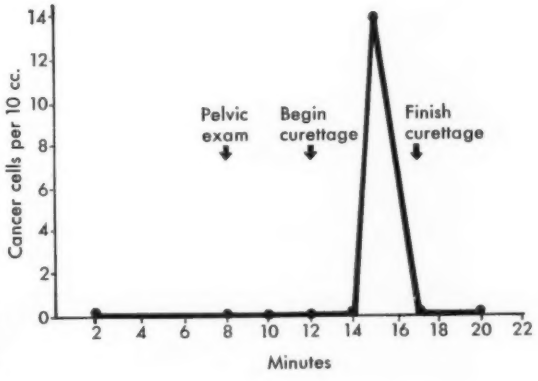


◀ Curettage of malignant bone tumor.



Prostatic massage. ▶

◀ Uterine curettage.



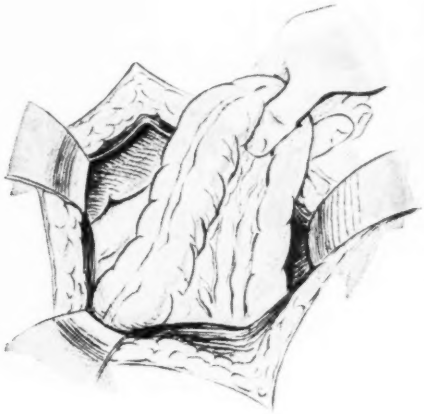

▶ Cancer cells in the inferior vena cava during dilatation and curettage. Adenoacanthoma of uterus.

## Operative Measures

Manipulation during skin preparation and mobilization of a tumor have been associated with showers of cancer cells in the blood stream. Contamination of operative areas by cancer cells has resulted in implantation recurrences. Examples are:

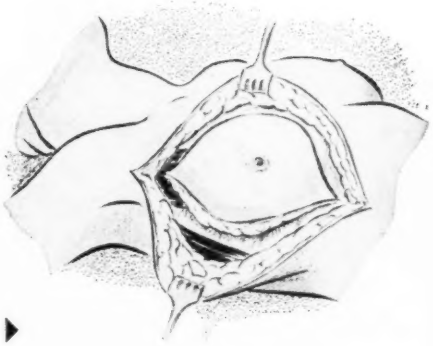
Skin preparation over a breast tumor[2]
Operative manipulation of bowel[8]
Operative manipulation of kidney[4]
Local seeding of wound during radical mastectomy[9]

◀ Skin preparation of breast.



Operative manipulation of bowel. ▶

◀ Operative manipulation of kidney.



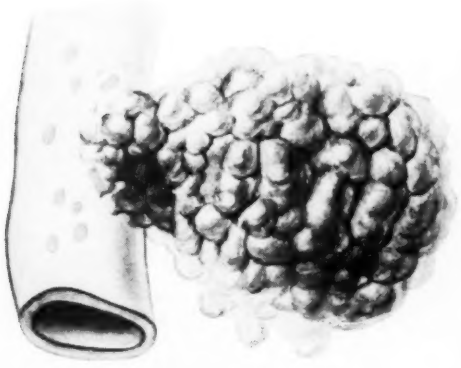
Local seeding of wound during radical mastectomy. ▶

# MECHANISMS OF DISSEMINATION

## Invasion

Many types of cancer are brought into contact with the circulating blood by invasion of the wall and penetration into the lumen of veins.[1,10] In addition, invasion of lymphatic channels places cancer cells in the lymph for possible transport to veins.[11]

Manipulation incident to physical examination or operation may dislodge an intravascular tumor into the circulation.[12,13] An example is a tumor embolus recovered from the inferior vena cava during prostatic massage.[6]



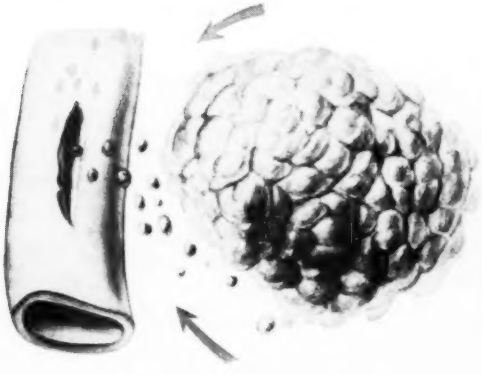
Invasion by cancer cells.

Tumor embolus.

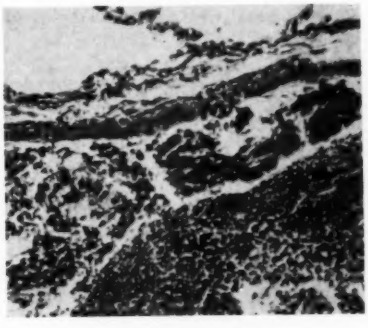
## Intravasation

This is the passage of cells into lacerated veins from adjacent disrupted normal or neoplastic tissue. Intravasation occurs under certain circumstances when the extravascular (tissue) pressure exceeds the intravascular pressure. Hence, intravasation is the reverse of extravasation.

Procedures such as transurethral resection,[6] incisional biopsy,[5] or curettage of deep-seated tumors,[7] in contrast to biopsy of superficial tumors, may disseminate cancer by intravasation. An example is a bone-marrow and tumor embolus found within the pulmonary artery.[14]



Intravasation of cancer cells.

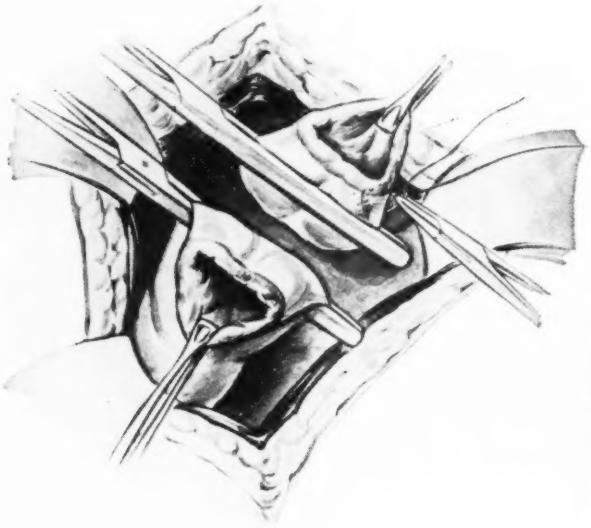


*(Courtesy of the Mayo Clinic.)*

## Implantation

When viable cancer cells are seeded on suitable tissue, some may survive and grow. This type of recurrence must be distinguished from that resulting from incomplete excision.[12]

During operation, the wound, body cavities, or lumen of hollow viscera may be contaminated with cancer cells by implantation. An example is a suture at a colon anastomosis surrounded by recurrent tumor.[15]



Implantation of cancer cells.

# PREVENTIVE MEASURES

Most deaths from cancer result from dissemination. We cannot predict which disseminated cells will produce metastases. Any measures which reduce dissemination will reduce metastases and recurrences.

## To Reduce Dissemination

Palpate *gently* all tumors during physical examination and operative manipulation.

Minimize the use of local anesthetic, thereby minimizing the possibility of intravasation or implantation or both.

Minimize biopsies of certain tumors.

Avoid massage of suspected prostatic cancer.

Avoid dilatation and curettage when the diagnosis can be established by other means.

Destroy the surface of ulcerating cancer immediately before excision.

Use protective pads on wound edges.

Irrigate wounds and bowel lumen with cancerocidal agents after resection.

Use wash basins containing a cancerocidal agent.

Use properly placed incisions to permit early vascular ligation.

Ligate artery and vein of a tumor before operative manipulation.

Ligate bowel proximal and distal to cancer.

Use tourniquets on extremities bearing cancer.

Use antiseptic solution for skin preparation rather than the more vigorous soap and water preparation.

Change instruments, gowns, gloves, etc. before moving from a cancer-contaminated area to a "clean" area.

## REFERENCES


1. Willis, R. A.: The Spread of Tumors in the Human Body. London, Butterworth and Company, Ltd., 1952.
2. Long, L., Jonasson, O. M., Roberts, S. S., McGrath, R., McGrew, E. and Cole, W. H.: Cancer cells in the blood: Results of a simplified isolation technique. A.M.A. Arch. Surg. 80:910, 1960.
3. Grove, W. J. et al.: Unpublished data, 1960.
4. Roberts, S. S., Watne, A., McGrath, R., McGrew, E. and Cole, W. H.: Technique and results of isolation of cancer cells from the circulating blood. A.M.A. Arch. Surg. 76:334, 1958.
5. Cole, W. H., McDonald, G. O., Southwick, H. W. and Roberts, S. S.: Dissemination of Cancer and Preventive Measures. New York, Appleton-Century-Crofts, Inc. To be published.
6. Jonasson, O. M., Long, L., Roberts, S. S. and McDonald, J.: Cancer cells in the circulating blood during operative management of genitourinary tumors. J. Urol. 85:1, 1961.
7. Roberts, S. S., Long, L., Jonasson, O. M., McGrath, R., McGrew, E. and Cole, W. H.: The isolation of cancer cells from the blood stream during uterine curettage. Surg. Gynec. & Obst. 111:3, 1960.
8. Turnbull, R. B., Jr.: Personal communication.
9. Smith, R. R., Thomas, L. B. and Hilberg, A. W.: Cancer cell contamination of operative wounds. Cancer 11:53, 1958.
10. Walther, H. E.: Krebs Metastasen. Basel, Benno Schwabe & Co., 1948.
11. Watne, A., Hatiboglu, I. and Moore, G. E.: A clinical and autopsy study of tumor cells in the thoracic duct lymph. Surg. Gynec. & Obst. 110:339, 1960.
12. Cole, W. H., Packard, D. and Southwick, H. W.: Carcinoma of the colon with special reference to prevention of recurrence. J.A.M.A. 155:1549, 1954.
13. Fisher, E. R. and Turnbull, R. B., Jr.: The cytologic demonstration and significance of tumor cells in the mesenteric venous blood in patients with colorectal carcinoma. Surg. Gynec. & Obst. 100:102, 1955.
14. DeLand, F. H. and Bennett, W. A.: Death due to bone marrow and tumor embolization in the absence of fracture: Report of a case. A.M.A. Arch. Path. 63:13, 1957.
15. Cole, W. H., McDonald, G. O. and Roberts, S. S.: Dissemination of cancer and its prevention. J. Roy. Coll. Surg. Edinburgh 4:218, 1959.

# CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

*Edited by William J. Donnelly, M.D., Chief, Section of Hematology*

# Recurrent Jaundice and Coma

***Case Report***

In October 1955, a 61 year old white Jewish male office employee was admitted to a private hospital in a comatose condition. On the day of admission, he had awakened feeling "shaky, nervous and faint." During the day he had become somnolent, and at 9 P.M. his wife had found him in a coma.

The patient had no history of head trauma, chest pain, diaphoresis or dyspnea. He had been taking 30 to 35 units of protamine zinc insulin daily for three years. Results of morning urine sugar determinations, made with CLINITEST® Reagent Tablets, had been consistently negative. For six months before hospitalization, his feet had swelled daily, but the swelling had subsided during the night. Accompanying dyspnea, orthopnea, chest pain and palpitation were denied. For three months before admission, the patient's urine had been dark orange in color. A decrease in appetite had been noted for two weeks before admission, but there had been no other gastrointestinal symptoms. After a two week hospitalization, the patient was transferred to Hines Veterans Administration Hospital for further care. At the time of this first admission to Hines, he complained only of weakness.

Diabetes had been diagnosed in this patient in 1952 and was initially controlled with 20 units of protamine zinc insulin daily. Fifteen years previously, his physician had told him he had an enlarged spleen. The patient had experienced easy bruising for many years. His mother had died of diabetes at the age of 87. Two siblings died in childhood of unknown causes; four were living and well. Previous jaundice or contact with hepatotoxins was denied. Intake of alcoholic beverages had never exceeded one bottle of beer per week.

When admitted to Hines, the patient appeared well developed but chronically ill. He seemed to comprehend questions quite well, but he answered in a rambling manner. His temperature was 98.8° F., pulse 88 and regular, respirations 20, and blood pressure 144/72. The scleras were icteric. The heart was normal except for a grade 2 blowing systolic murmur heard over the precordium. The liver was palpable 12 cm. below the right costal margin, firm, uniform in consistency, and nontender. The spleen was palpable 14 cm. below the left costal margin and was firm

and nontender. Many pigmented nevi were seen in the skin of the trunk. The examiner noted increased pigmentation of the skin and areolae, but the patient denied any change in the color of his skin, and said that his entire family was dark-skinned.

Laboratory data recorded during this hospitalization showed trace to 2 plus proteinuria, increased urinary urobilinogen, negative results of a serologic test for syphilis, and a normal chest film. An electrocardiogram showed borderline results. Erythrocyte count was 3.7 million; leukocyte count was 7900 per cubic millimeter, and differential leukocyte count was normal. Bleeding and coagulation times were normal. Nonprotein nitrogen was 36 mg., and fasting blood sugar level varied from 140 to 202 mg. per 100 ml. Serum total protein was 8.8 gm. per 100 ml.; albumin was 2.4 gm. Cephalin-cholesterol flocculation was 4 plus, thymol turbidity 13 units, alkaline phosphatase 6.6 Bodansky units, bilirubin 7.8 mg., and cholesterol 256 mg. per cent. The sulfobromophthalein sodium retention was 40 per cent, and the prothrombin time was 13 seconds. A biopsy of the liver was performed on November 4, 1955.

The diabetes was initially treated with a 2300 calorie diabetic diet, but persistent 2 to 3 plus glycosuria necessitated the daily administration of 10 units of NPH insulin. The jaundice subsided during the first week of hospitalization, but lethargy persisted. The patient was discharged to the care of his family physician.

From 1955 to 1958, inclusive, the patient was admitted to Hines nine times. On three occasions, he had pneumonia of the left lower lobe, which responded well to penicillin. He was hospitalized twice because of poor diabetic control, characterized by 4 plus glycosuria and 1 to 2 plus ketonuria, but he responded quickly to hydration and adjustment of insulin dosage. The other periods of hospitalization were required because of episodes of lethargy accompanied by flapping tremor of the hands. These episodes were treated with a low-protein diet and antibiotics. In July 1957, an electroencephalogram revealed "mild slowing within normal limits." Repeated bone-marrow aspirations demonstrated slight erythroid hyperplasia; special staining of the marrow for iron revealed normal iron stores. Results of a biopsy of the skin and of an esophagoscopic examination were negative. Serum iron varied between 26 and 188 $\mu$g. per 100 ml. Hepatosplenomegaly, icterus and moderate ankle edema persisted.

At the time of his last hospitalization, on March 14, 1958, the patient was unable to give a history. His wife said that he had become quite irritable about three days before admission. He had refused to eat, and his wife had decreased the daily dose of insulin. She said that his urine sugar level had been running a trace to 4 plus for three or four days before admission.

Examination revealed that the patient's temperature was 100° F., pulse 90, respirations 18, and blood pressure 140/70. He was not responsive to questioning. The scleras were icteric. There was pitting edema of the sacrum and the flanks. The heart was normal. The liver and the spleen were felt 8 and 4 cm., respectively, below the costal margin. An abdominal fluid wave was present. Neurologic examination gave negative results. There was severe edema of the lower extremities, as well as edema of both arms. A chest film showed resolving bronchopneumonia. Urinalysis revealed an acid urine, specific gravity of 1.010, 4 plus proteinuria, many white blood cells, and red blood cells. Blood sugar was 207 mg. on admission and 354 mg. on the following day. Nonprotein nitrogen was 58 mg. Carbon dioxide-combining power was 21.2 mEq. per liter on March 15. An electrocardiogram showed abnormal but nonspecific changes. Hematocrit was 32 per cent and hemoglobin 12.5 gm.; the leukocyte count was 5300. The patient was given glucose intravenously and a low-protein diet, but the coma persisted until he died quietly on March 17.

### *Discussion*

DR. HYMAN J. ZIMMERMAN (professor and chairman, department of medicine, Chicago Medical School, Chicago): Diabetics who are receiving insulin may lose consciousness because of either diabetic coma or hypoglycemia.

Rapidly developing coma is not diabetic coma. Even in children it is rare for diabetic coma to develop over a 24 hour period. The patient who is all right at night but a little stuporous the next morning is much more likely to have hypoglycemia. Of course, we cannot diagnose hypoglycemic coma in this case without considering other causes of coma; however, the absence of a history of head trauma, chest pain, diaphoresis and dyspnea tends to exclude the kind of medical accidents that can lead to coma.

This patient had no heart failure, yet he had edema daily, which disappeared with a night's rest. The bilirubin in the urine accounted for its dark orange color. The early finding of an enlarged spleen is interesting and was the first clinical evidence of hepatic disease in this case. A long course before development of jaundice in a patient with splenomegaly secondary to cirrhosis is unusual. Therefore, I would consider other causes for the splenomegaly in this patient. He might have had Gaucher's disease, which is particularly pertinent in a Jewish patient, or a sarcoidosis which had burned itself out by this time but had left some splenomegaly. The "easy bruising" which this man had had for many years could have represented a plasma coagulation defect or a defect in formed elements. We do not know whether he had a hypersplenic thrombocytopenia, a defect in the thromboplastin-forming part of coagulation, or some other coagulation defect.

That the liver was not tender when the patient was admitted to Hines in 1955 is not surprising. Intrinsic hepatic disease is rarely accompanied by real tenderness. Patients with hepatitis do not like being compressed in that area; however, they feel nausea and discomfort rather than real pain. In cirrhosis, hepatic tenderness is quite unremarkable unless there is rapidly developing fatty metamorphosis. The chief diseases which cause hepatic tenderness are congestive heart failure, rapidly extending metastatic carcinoma, and amebic hepatitis. Chiari's disease, which is analogous to heart failure, also may produce hepatic tenderness.

The presence of pigmentation in the skin and areolae of a patient who has diabetes and an enlarged liver and who has rapidly gone from being "shaky" and nervous into a comatose state properly suggests hemochromatosis. However, jaundice is not common in hemochromatosis unless the frequent hepatoma develops as a complication and is located so that it obstructs the intrahepatic biliary tree. Furthermore, this patient's serum iron levels were below the range ordinarily expected in hemochromatosis.

I would like to discuss the possible findings of the biopsy of the liver. The laboratory data on the status of the liver would suggest an active postnecrotic cirrhosis. Globulin levels in the neighborhood of 6 gm. are almost unheard of with acute viral or toxic hepatitis; they are extremely rare, if found at all, in ordinary Laennec's cirrhosis. Such values would not be expected in patients with obstructive biliary tract disease, but they are characteristic of patients with active postnecrotic cirrhosis. Therefore, I would expect that the biopsy showed an active postnecrotic cirrhosis. I am also anxious to see the results of the biopsy in order to exclude hemochromatosis. Now, if the hunch that splenomegaly represented an antecedent and unrelated disease is right, the liver biopsy also may help us in other ways. If previous granulomatous disease had caused the splenomegaly, granulomas or remnants of them might be seen in the liver. If the patient had had Gaucher's disease, Gaucher's cells might be observed.

If this patient had not had diabetes, occurrence of pneumonia three times in three years might have indicated the presence of acquired hypogammaglobulinemia. However, with repeated infections and a total globulin level as high as this patient had, hypogammaglobulinemia could not have been considered unless he had had multiple myeloma, in which the globulin is immunologically ineffective.

The episodes of lethargy and flapping tremor of the hands, for which the patient was hospitalized several times, confirm my impression of the presence of parenchymal hepatic disease. One of the most important advances in the management and understanding of liver disease in the past 12 years was

the demonstration by Foley and Adams in 1949 that hepatic coma is preceded by a characteristic flapping tremor. A patient with jaundice and a flapping tremor should be considered to be in hepatic precoma.

Thus, this patient had chronic hepatic disease with episodes of what appeared to be impending hepatic coma. I presume that these episodes were treated with broad-spectrum, poorly absorbed antibiotics and with protein restriction. The negative results of the skin biopsy help to exclude hemochromatosis, since about half the patients with hemochromatosis have hemosiderin deposits demonstrable on skin biopsy. However, hemochromatosis in this patient is not excluded as much by the absence of these deposits as by the normal serum iron level.

The patient's irritability for three days before his hospitalization in 1958 is significant. It is well known that hepatic coma may be anticipated when a patient with liver disease shows a personality change. Long before the flapping tremor, the value of the blood ammonia level determinations, or the electroencephalographic abnormality was recognized, clinicians interested in liver disease knew that when a previously agreeable patient became obstreperous impending coma was likely.

When edema and ascites are prominent in a patient with or without intrinsic liver disease, we must include the possibility of hepatic vein occlusion (Chiari's disease). This is a difficult diagnosis to establish during life, but often the thrombosis extends from the hepatic vein to the inferior vena cava. The edema level may then extend up to the point of occlusion and also may involve the abdominal wall. The demonstration that femoral venous pressure is considerably higher than antecubital venous pressure is suggestive evidence of occlusion of the inferior vena cava.

I do not believe the combination of liver disease and diabetes in this patient was hemochromatosis. I think that he had diabetes and an acquired liver disease. Was the jaundice caused by a disease of the hepatic parenchyma or an atypical obstructive disease of the extrahepatic biliary tree? On the basis of the evidence, I believe we may conclude that it was parenchymal disease. I doubt that this man had either viral or toxic hepatitis when first seen. That he could have had hepatitis which had begun insidiously three or four months before and have had an active postnecrotic cirrhosis when first examined, I find very believable. We must consider the possibility that he had a much earlier hepatitis, with a late activation of a postnecrotic cirrhosis.

We now know that the incidence of hepatoma in postnecrotic cirrhosis is 10 to 15 per cent, whereas it is 1 to 3 per cent in Laennec's cirrhosis. Therefore, every patient with postnecrotic cirrhosis becomes a very good candidate for hepatoma. This patient had such severe edema that the possibility of a hepatoma is even greater. We know that more than half of the patients with hepatomas have invasion of the hepatic or portal veins, or the metastases progress up the vena cava into the auricle. It is quite conceivable that this patient also may have had a hepatoma.

The diagnoses I would make in this case are diabetes; active postnecrotic cirrhosis in 1955, with varying degrees of persistent activity; a good probability of a hepatoma; and, terminally, perhaps Chiari's syndrome, probably due to neoplastic invasion of the hepatic veins by hepatomatous tissue, with hepatic coma.

DR. GLOUCESTER A. PRICE (assistant chief, hematology section): Do you think that the pigmentation in postnecrotic cirrhosis differs from that in Laennec's cirrhosis?

DR. ZIMMERMAN: I think that we see more patients with pigmentation in the alcoholic group, but my opinion is not based on observation of the pigment in skin biopsies. Most of the reports in the past have not differentiated Laennec's and postnecrotic cirrhosis.

DR. CALVIN RADIN (staff physician, medical service): Do you think this patient's diabetes was on the basis of pancreatic or liver disease? If you are positive that he did have cirrhosis, I would like to know the incidence of frank diabetes in postnecrotic cirrhosis.

DR. ZIMMERMAN: This man had clinical diabetes, treated with insulin for three years, before any real evidence of hepatic disease appeared. He also had a family history of

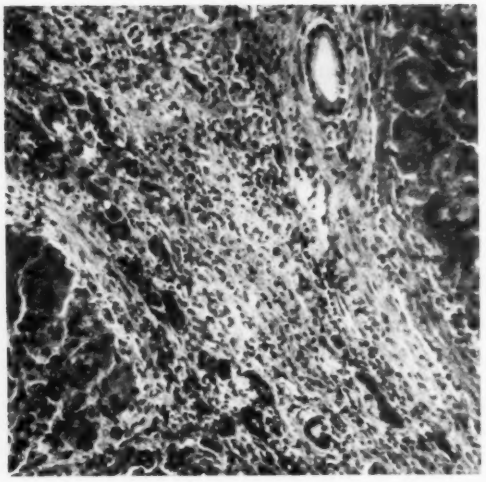


FIGURE 1. Photomicrograph of liver biopsy specimen showing extensive portal fibrosis and proliferation of bile ducts. The bile ducts and the liver cord cells contain abundant hemosiderin. (Iron hematoxylin stain.)

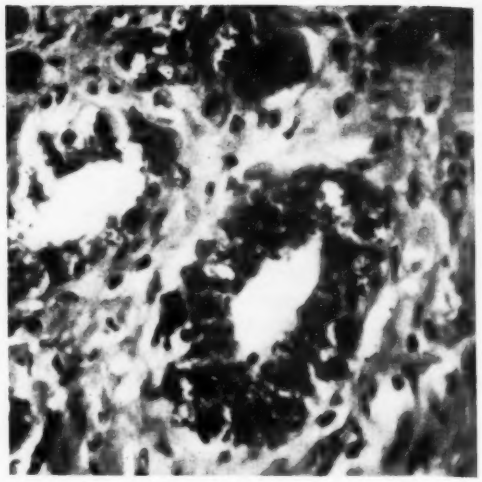


FIGURE 2. High-power photomicrograph of a bile duct showing heavy deposition of hemosiderin. (Iron hematoxylin stain.)

diabetes. I think this was the usual type of diabetes. Now, you asked about the status of hepatic pseudodiabetes. I believe that there is still some evidence of what might be called hepatic pseudodiabetes. In some patients with liver disease, a derangement of carbohydrate metabolism occurs which may mimic diabetes, not only with an abnormal glucose tolerance but also with an elevated fasting blood sugar level. We found that 22 of approximately 150 cirrhotic patients had had elevated fasting blood sugar levels. The basis of this is not clear. The simplest explanation to advance today would be that the same alcoholism or the same way of life that leads to cirrhosis also produces a high incidence of pancreatitis. Thus, many of these patients may have simply the diabetes associated with chronic pancreatitis. Similarly, transient diabetes may be caused by episodes of acute pancreatitis.

A fascinating study was done by a group working with Dr. Rachmiel Levine a few years ago. They found that a hepatectomized dog showed an impairment of peripheral glucose utilization. It may well be that liver disease in some unknown way impairs peripheral utilization of glucose. If so, there may indeed be hepatic pseudodiabetes. One of my friends whimsically suggested, with no good evidence, that perhaps the impaired metabolism of glucocorticoids by the diseased liver may yield the diabetogenic effect of an endogenous hyperadrenocorticism.

DR. MYRON E. RUBNITZ (chief, laboratory service): Microsections of the liver biopsy performed in 1955 showed a severe perilobular fibrosis and a heavy infiltration by inflammatory cells and pigment. Examination of the sections at a higher magnification showed a heavy deposition of this pigment in the parenchymal cells of the liver, in the Kupffer cells, and in the epithelium of the bile ducts. In sections stained with Prussian blue, the pigment was found to be hemosiderin (figures 1 and 2).

Dr. Zimmerman, would you care to comment on the findings in the liver biopsy?

DR. ZIMMERMAN: There is no doubt that this was either exogenous or endogenous hemochromatosis. Since I believe that exogenous hemochromatosis rarely complicates postnecrotic cirrhosis and that constitutional hemochromatosis often resembles postnecrotic cirrhosis, I would say that this looks like constitutional hemochromatosis. I cannot ex-

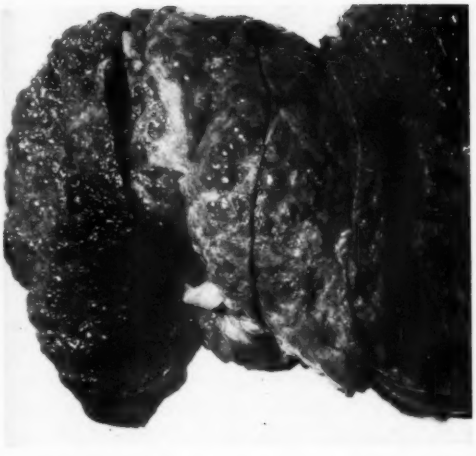


FIGURE 3. Photograph of liver showing irregular, nodular appearance.

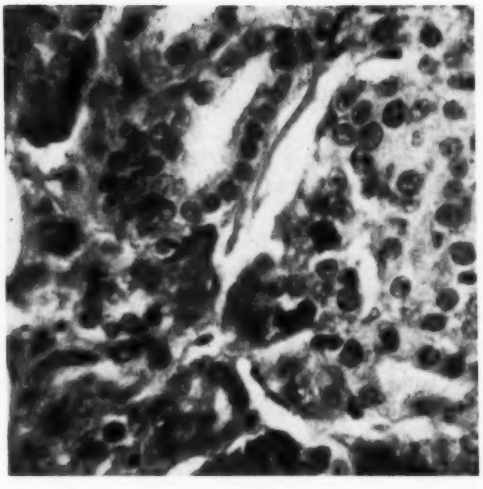


FIGURE 4. Photomicrograph of pancreas showing hemosiderin in acinar structures (upper left) and islet tissue (right center).

plain the surprisingly low serum iron levels. In none of the reported cases of hemochromatosis have the serum iron levels been below 150 μg., but what has been shown is more important than laboratory data. We can always be led astray by one or two laboratory findings. I have to agree that this patient had hemochromatosis, but I still think he died in hepatic failure. Since the incidence of hepatoma in hemochromatosis is about 8 to 10 per cent, a hepatoma would still be a good additional possibility.

DR. LIONEL BERNSTEIN (assistant director, professional services for research): About 25 years ago an investigator created siderosis of tissues by ligating the pancreatic duct in animals. Could this disease have started as a chronic pancreatitis, with a secondary increase in iron absorption?

DR. ZIMMERMAN: This is certainly one of the theories of the method by which acquired hemochromatosis may develop in the alcoholic. Since this case does not look like Laennec's cirrhosis to me, I would be surprised if this man had chronic pancreatitis on some basis other than hemosiderin deposits.

DR. E. O. WILLOUGHBY (assistant chief, medical service): Would you care to make any prediction about the heart?

DR. ZIMMERMAN: Congestive heart failure is fairly common in hemochromatosis, but this man had neither very impressive heart failure nor any conduction defects. However, I would not be surprised if he had hemosiderin in the heart.

DR. RUBNITZ: At autopsy, the spleen weighed 1000 gm.; it was firm and dark red-brown in color. The pancreas grossly appeared normal. The lungs showed evidence of bronchopneumonia in the right middle and lower lobes. The liver was contracted, weighed 1,050 gm., and was grossly cirrhotic with large nodules separated by wide bands of connective tissue, suggesting a postnecrotic type of cirrhosis (figure 3).

Microsections of the liver showed that these nodules were regenerative, with no evidence of normal lobular architecture. A small amount of fat was scattered throughout the lobules. There was a marked proliferation of bile ducts within the extensive areas of fibrosis. Specially stained sections of the liver showed iron deposits throughout all areas of the hepatic lobules and in the perilobular fibrous tissue. There was much hemosiderin in the epithelium of the bile ducts and in the parenchymal cells of the liver. There was also a heavy deposition of iron in the Kupffer cells.

Microsections of the pancreas showed slight fibrosis, some chronic inflammatory infiltrates, and a moderate amount of chronic pancreatitis. Throughout the pancreas, in both acinar structures and islet tissue, there was a brownish-colored pigment. The sections that stained for iron showed that this pigment was hemosiderin (figure 4).

Microsections of the heart showed hemosiderin pigment throughout the myocardium. Microsections of the lung confirmed the grossly evident bronchopneumonia.

DR. ZIMMERMAN: Thank you very much, Dr. Rubnitz. This was a fascinating case. At the bedside, I would have made the same diagnosis that I just made. Jaundice waxing and waning over a three year period is seen infrequently in hemochromatosis. This patient may have had recurrent episodes of necrosis. Extensive necrosis occasionally occurs in the course of hemochromatosis. It generally has been ascribed to alterations in blood flow and considered to be ischemic necrosis. Some recent animal experimentation would indicate that the deposition of excessive iron in tissues results in local necrosis. I do not think that this patient had exogenous hemochromatosis or hemochromatosis as a sequela to cirrhosis, I think he had classic endogenous (constitutional) hemochromatosis.

### *Summary of Diagnoses*

*Clinical diagnoses*—(1) Hemochromatosis (by liver biopsy); (2) hepatic coma.

*Dr. Zimmerman's diagnoses*—(1) Diabetes mellitus; (2) postnecrotic cirrhosis; (3) hepatoma (?); (4) Chiari's syndrome (?); hepatic coma.

*Pathologic diagnoses*—(1) Hemochromatosis, involving liver, pancreas and heart; (2) bronchopneumonia, right middle and lower lobes of the lung.

## Books Received

**Books received are acknowledged by listing. As space permits, selected books are reviewed more extensively. Reviews in this issue start on page A-103; additional listings appear on page 110.**

**Biochemistry for Medical Students.** By William Veale Thorpe, Ph.D., Reader in Chemical Physiology, University of Birmingham, Birmingham, England. Ed. 7. 552 pages with 50 illustrations. 1960, J. & A. Churchill Ltd., London. Distributed by Little, Brown & Company, Boston. $9.00.

**Parkinsonism;** Its Medical and Surgical Therapy. By Irving S. Cooper, M.D., Professor of Research Surgery, New York University School of Medicine, New York. 239 pages, illustrated. 1961, Charles C Thomas, Springfield, Illinois. $16.50.

**The Eye in General Practice.** By C. R. S. Jackson, F.R.C.S.E., Ophthalmic Surgeon, Royal Infirmary, Edinburgh, Scotland. Ed. 2. 152 pages with 26 illustrations. 1960, E. & S. Livingstone Ltd., Edinburgh and London. Distributed by The Williams & Wilkins Company, Baltimore. $5.00.

**Haematology.** By R. B. Thompson, M.D., Senior Lecturer in Medicine, University of Durham Medical School, King's College, Newcastle-upon-Tyne, England. 306 pages, illustrated. 1961, J. B. Lippincott Company, Philadelphia and Montreal. $6.00.

**Management of Obstetric Difficulties.** Revised by J. Robert Willson, M.D., Professor of Obstetrics and Gynecology, Temple University School of Medicine, Philadelphia. Ed. 6. 687 pages with 323 illustrations. 1961, The C. V. Mosby Company, St. Louis. $16.50.

**Symptom Diagnosis.** By Wallace Mason Yater, M.D., Director, Yater Clinic, Washington, D. C., and William Francis Oliver, M.D., University of Southern California School of Medicine, Los Angeles. Ed. 5. 1,035 pages. 1961, Appleton-Century-Crofts, Inc., New York. $15.00.

**The Year Book of Endocrinology (1960-1961).** Edited by Gilbert S. Gordan, M.D., Chief of Endocrine Clinics, University of California School of Medicine, Berkeley-San Francisco. 408 pages with 69 illustrations. 1961, Year Book Medical Publishers, Inc., Chicago. $8.00.

**A Manual of Cutaneous Medicine.** By Donald M. Pillsbury, M.D., Chairman, Department of Dermatology, Walter B. Shelley, M.D., Professor of Dermatology, and Albert M. Kligman, M.D., Professor of Dermatology, University of Pennsylvania School of Medicine, Philadelphia. 430 pages, illustrated. 1961, W. B. Saunders Company, Philadelphia and London. $9.50.

**Advances in Thyroid Research.** Transactions of the Fourth International Goitre Conference. Edited by Rosalind Pitt-Rivers, National Institute for Medical Research, Mill Hill, London, England. 537 pages, illustrated. 1961, Pergamon Press Ltd., London. $20.00.

# Editorials

Postgraduate Medicine

*Editor-in-Chief:*
CHARLES W. MAYO, M.D.

*Contributing Editor:*
MORRIS FISHBEIN, M.D.

*Executive Editor:*
SYLVIA COVET

## BRAIN RESEARCH

At a meeting held at UNESCO House, Paris, October 2 and 3, 1959, a study group outlined a plan for an organization to be called the Interdisciplinary Brain Research Organization. This plan was forwarded to the Council of International Organizations of the Medical Sciences (CIOMS), which subsequently established the International Brain Research Organization (IBRO). Over 250 scientists in more than 30 different countries were approached for their approval. The overwhelming majority gave their consent, and the organizational meeting was held in Paris at the UNESCO House in October 1960.

This organization will foster fundamental scientific research contributing to an understanding of the brain, normal and abnormal. Its functions will include the establishment of fellowships and the exchange of scientific workers, promotion of world-wide education in brain research, extension of existing laboratory facilities, distribution of information, and the holding of symposia, conferences and meetings. Scientists will be drawn from various disciplines. Executive officers already have been chosen; committees have been established to report on various phases of problems in research on the brain, and panels have been set up for the consideration of such problems.

The Secretariat may be addressed at IBRO—UNESCO, 2 Place de Fontenoy, Paris, France.

The Brain Research Foundation, which has been carrying on its activities in the United States, has now purchased a building and is in the process of establishing a center in what was once the Chicago Memorial Hospital. This center eventually will house clinics devoted to epilepsy, cerebral palsy, mental retardation, cerebrovascular disease, parkinsonism, narcolepsy, multiple sclerosis, migraine, neuroses, psychoses, alcoholism and drug addiction. Facilities will be available for housing patients referred by physicians and health agencies, and indigent patients will be treated to the maximum of financial resources. The first step is the establishment of an epilepsy clinic with an electroencephalographic laboratory. Since this phase of the work is headed by Dr. Frederic A. Gibbs, professor of neurology, University of Illinois College of Medicine, a high quality of investigation may be anticipated.

The Brain Research Foundation may be addressed at 39 South LaSalle, Suite 424, Chicago 3, Illinois.

MORRIS FISHBEIN

## ADRENOCORTICAL RESPONSE OF BANTU AND EUROPEANS TO SURGICAL STRESS

BANTU react to surgical conditions, especially to acute abdominal emergencies (peritonitis, strangulated hernia or intestinal obstruction), more mildly than do Europeans. Among the Bantu a discrepancy often is apparent between the serious condition found at operation and the relative absence of shock, fever, pain or rigidity. Dr. L. Parkinson and his associates[1] at Elisabethville, Belgian Congo, compared the response of the adrenal cortex to surgical stress in Europeans and Bantu.

After surgery, the adrenals secrete an increased amount of 17-hydroxycorticosteroids. The magnitude and duration of the rise in the total urinary content of these substances are closely related to the degree of trauma and to the patient's course. The highest figures are encountered on the first and second days after operation. By the fourth day the daily excretion usually returns to normal. The eosinophil count falls to low or zero values a few hours after operation, remains low for two to three days, and swings back to preoperative levels when the excretion of corticosteroids returns to normal.

The adrenal response to surgical stress, determined by the corticosteroid excretion and the eosinophil count before and after operation, was compared in 53 Bantu and 53 Europeans. There were close parallels in the two series regarding sex and type of operation.

Before operation the corticosteroid excretion in European and Bantu women was almost identical. The values in European men were normally about 25 per cent higher than those in the Bantu men. The suprarenals of East African Bantu men are smaller than those of North American white people because of a difference in cortical weight unrelated to total body weight.

Urinary corticosteroid excretion in the 72 postoperative hours was about 30 per cent lower in the Bantu than in the Europeans, irrespective of sex. The eosinophil count also showed less response to surgery in the Bantu. No relationship could be found between postoperative urine volume and steroid excretion in either race.

The investigators suggest that a poor nutritional state might affect adrenal secretion. The diet of most Africans is poor in proteins, and their adrenal reserve might therefore be low. Many have parasitic diseases which may produce a subclinical asthenia, and asthenic subjects have a low urinary steroid excretion.

The clearance rate of hydrocortisone is decreased in liver disease. Hepatic patients have a lower daily excretion of corticosteroids. Liver deficiencies are common in Africans, due to parasitic diseases and malnutrition. Since the liver is concerned with the hydrogenation and conjugation of the free plasma steroids and since 90 to 95 per cent of the urinary steroids are conjugate, the presence of liver deficiencies in the Bantu could explain some of the results.

MORRIS FISHBEIN

### REFERENCE

1. PARKINSON, L., GHYOOT, E., VAN VLIERBERGHE, R. and BONE, G.: Adrenocortical response of Bantu and Europeans to surgical stress. Tr. Roy. Soc. Trop. Med. & Hyg. 54:366-372 (July) 1960.

Haldrone is a potent synthetic corticosteroid with marked anti-inflammatory activity. In steroid-responsive conditions, it provides predictable anti-inflammatory effects with a minimum of untoward reactions. Gratifying response has been observed in patients transferred from other corticosteroids to Haldrone. There is relatively little adverse effect on electrolyte metabolism. With Haldrone, sodium retention is unlikely, psychic effects are minimal, and there appears to be freedom from muscle weakness and cramping.

***Haldrone, 2 mg., is approximately equivalent to***

| | | |
|---|---|---|
| Cortisone | 25 | mg. |
| Hydrocortisone | 20 | mg. |
| Prednisone or prednisolone | 5 | mg. |
| Triamcinolone or methylprednisolone | 4 | mg. |
| Dexamethasone | 0.75 | mg. |

Although the incidence of significant side-effects is low, the usual contraindications to corticosteroid therapy apply to Haldrone.

***Supplied in bottles of 30, 100, and 500***

Tablets Haldrone, 1 mg., Yellow (scored)
Tablets Haldrone, 2 mg., Orange (scored)

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.
140041

# New *for your armamentarium*

*Information published in this department is supplied by the manufacturers of the products described.*

### • CASCADE TANKS

DESCRIPTION: Constructed of stainless steel, these x-ray film-processing tanks employ a jet-spray nozzle for sludge-free water circulation. The 14 basic tank models and complete accessories for 107 variations fulfill the processing requirements of any type of medical x-ray operation.
PRODUCER: Picker X-Ray Corporation, White Plains, N.Y.

### • ELECTRELL CREAM

DESCRIPTION: For use in electrocardiography and electroencephalography, this scientifically blended cream solubilizes skin oils, thus providing a good conducting medium without variance. It is easily applied and not greasy, and it will not corrode electrodes.
DISTRIBUTOR: General Electric X-ray Dept., Milwaukee.

### • AVAZYME® TABLETS

PURPOSE: To treat inflammation and edema.
COMPOSITION: Each enteric-coated tablet contains crystalline chymotrypsin with a proteolytic activity of approximately 20 mg.
HOW SUPPLIED: Bottles of 48.
PRODUCER: Wampole Laboratories, Stamford, Conn.

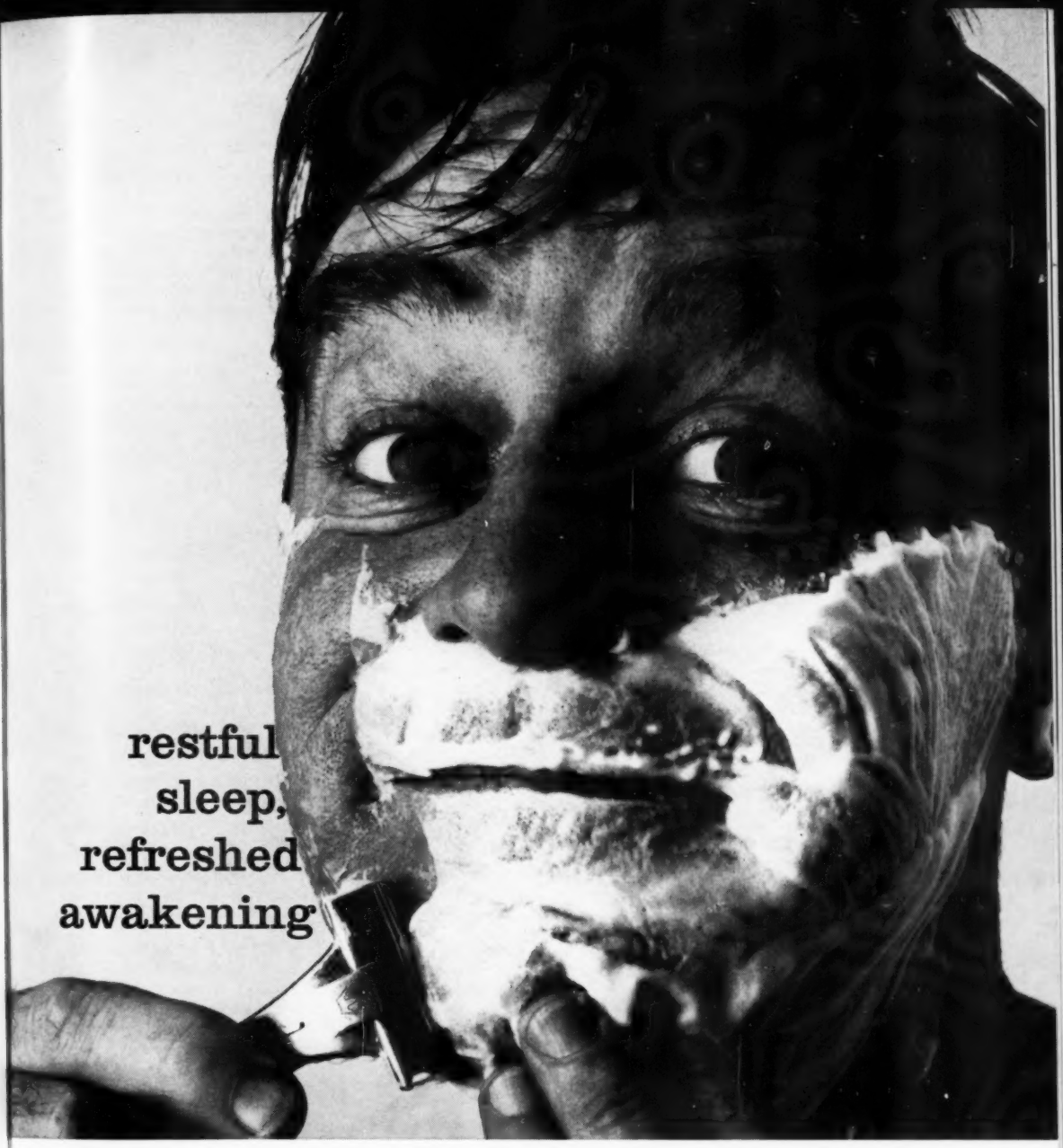
### • ATARAX® PARENTERAL SOLUTION (New Dosage Form)

DESCRIPTION: This tranquilizing agent is now available in 10 cc. vials, each cubic centimeter containing 50 mg. hydroxyzine hydrochloride.
PRODUCER: J. B. Roerig and Company, Division, Chas. Pfizer & Co., Inc., New York.

### • LYOPHRIN®

PURPOSE: To treat simple glaucoma.
COMPOSITION: Levoepinephrine bitartrate.
CAUTION: This agent is contraindicated in patients with narrow-angle glaucoma. Gonioscopy should be performed on all patients before the drug is administered. Use of Lyophrin should be discontinued if the solution becomes darkly colored.
DOSAGE AND ADMINISTRATION: 1 drop of Lyophrin, reconstituted as a 2 per cent solution. This agent is best administered at bedtime.
HOW SUPPLIED: Packages of one vial of sterile lyophilized levoepinephrine bitartrate and one 5 cc. bottle of Lyophrin diluent.
PRODUCER: Alcon Laboratories, Inc., Fort Worth.

*(Continued on page A-96)*




After a night of deep, refreshing sleep—this is the promise of Noludar 300. One capsule at bedtime acts quickly... eases your patient into sleep without pre-excitement, gives up to 6 or 8 hours of undisturbed sleep without risk of habituation, without toxicity or even minor side effects. Try Noludar 300 for your next patient with a sleep problem. Chances are he'll tell you

## "I slept like a log"

# NOLUDAR® 300

brand of methyprylon

*300-mg capsules*

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, New Jersey

### • NCG-METROX

DESCRIPTION: Containing 305 liters of oxygen (a 51 minute supply), this portable oxygen unit is regulated to supply from 3 to 12 liters per minute. Equipment includes a plastic mask with intake and exhaust valves, a carrying case, and a refilling adapter and wrench. Also available is a smaller model containing 56 liters of oxygen (a nine minute supply).
PRODUCER: Metrox, Inc., Pasadena and Wilmington, Del. Distributed by the National Cylinder Gas Division of Chemetron Corporation, Chicago.

### • DECHOLIN®-BB

PURPOSE: For treatment of gastrointestinal and biliary disturbances.
COMPOSITION: Each tablet contains:

| | |
|---|---|
| Butabarbital sodium | 15 mg. |
| Dehydrocholic acid (Decholin) | 250 mg. |
| Extract of belladonna | 10 mg. |

DOSAGE AND ADMINISTRATION: For adults, 1 or 2 tablets three times a day. Dosage may be continued for four to six weeks, with course repeated as necessary.
HOW SUPPLIED: Bottles of 100.
PRODUCER: Ames Company, Inc., Elkhart, Ind.

### • NEOSPORIN® AEROSOL

PURPOSE: Antibacterial therapy in skin infections.
COMPOSITION: This preparation contains:

| | |
|---|---|
| Polymyxin B sulfate (AEROSPORIN®) | 100,000 units |
| Zinc bacitracin | 8000 units |
| Neomycin sulfate | 100 mg. |

These agents are combined with an inert propellant of dichlorodifluoromethane and trichloromonofluoromethane.
CAUTION: Prolonged use may result in overgrowth of nonsusceptible organisms. Do not spray in the eyes.
DOSAGE AND ADMINISTRATION: Spray affected area for one second from a distance of 8 in.
HOW SUPPLIED: 90 gm. aerosol spray containers.
PRODUCER: Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N. Y.

### • LIBRAX®

PURPOSE: To treat gastrointestinal disorders associated with anxiety and tension.
COMPOSITION: Each capsule contains 5 mg. LIBRIUM® hydrochloride and 2.5 mg. QUARZAN® bromide.
CAUTION: This agent is contraindicated in patients with glaucoma, and it may cause urinary retention in patients with prostatic hypertrophy. The concomitant administration of Librax and other psychotropic agents is not recommended.
DOSAGE AND ADMINISTRATION: For adults, 1 or 2 capsules four times a day, taken before meals and at bedtime; for elderly and debilitated patients, not more than 2 capsules a day initially, to be increased gradually as needed and tolerated.
HOW SUPPLIED: Bottles of 50 and 500.
PRODUCER: Roche Laboratories, Division of Hoffmann-La Roche, Inc., Nutley, N. J.

### • MYLICON® TABLETS AND DROPS

PURPOSE: To relieve flatulence.
COMPOSITION: Each tablet and each 0.6 cc. contain 40 mg. methylpolysiloxane.
DOSAGE AND ADMINISTRATION: For adults, 1 tablet to be chewed after each meal and at bedtime; for infants, 0.3 to 0.6 cc. with each feeding.
HOW SUPPLIED: Tablets in bottles of 100 and 500; drops in dropper bottles of 30 cc.
PRODUCER: The Stuart Company, Pasadena.

### • BEJEX®

PURPOSE: Dietary supplement.
COMPOSITION: Therapeutic amounts of six B complex vitamins and vitamin C, with benzyl alcohol, methylparaben and propylparaben as preservatives and formaldehyde sodium sulfoxylate and sodium sulfide as stabilizers in water for injection.
DOSAGE AND ADMINISTRATION: 5 ml. daily, either intramuscularly or intravenously. Intramuscular injections should be made deep in a large muscle mass to assure rapid absorption and to minimize pain. Intravenous injections should be made slowly, or the intravenous dose may be added to an infusion of 5 per cent dextrose in sterile water, sodium chloride injection, or 5 per cent dextrose in sodium chloride injection.
HOW SUPPLIED: 5 ml. UNIVIAL® containers.
PRODUCER: Abbott Laboratories, North Chicago.

### • TOLFERAIN®

PURPOSE: Hematinic therapy.
COMPOSITION: Each sustained-release tablet contains 300 mg. ferrous fumarate, which provides 100 mg. elemental iron.
DOSAGE AND ADMINISTRATION: 1 tablet daily; for severe anemic states, 2 tablets daily.
HOW SUPPLIED: Bottles of 100 and 1000.
PRODUCER: B. F. Ascher & Company, Inc., Kansas City, Mo.

# THE MEDICAL *Bookman*

## ► TEXTBOOK OF MEDICAL PHYSIOLOGY

By Arthur C. Guyton, M.D., Chairman, Department of Physiology and Biophysics, University of Mississippi School of Medicine, Jackson. Ed. 2. 1,179 pages with 774 illustrations. 1961, W. B. Saunders Company, Philadelphia and London. $15.50.

This very extensive volume begins with a section on cell physiology and ends with a discussion of radiation. Topics are covered with a conciseness and clarity that probably results from observations and comments on the first edition of this text. Many figures presented in the first edition have been changed to fit this new presentation, and more than 200 additional figures have been included.

The human body is presented as a single functioning organism controlled by many regulatory systems, with emphasis on the "automaticity of the life processes." The bibliographies are plentiful and well selected and cover almost every phase of physiology.

I. P. F.

## ► UROLOGY IN GENERAL PRACTICE

By Ian Parton, F.R.C.S., Assistant Urologist, Auckland Hospital, Auckland, New Zealand. 304 pages, illustrated. 1960, Butterworth & Co. Ltd., London and Toronto. $9.00.

Intended for general practitioners, this well-written book admirably fulfills its purpose. No attempt is made to burden the reader with unnecessary details, and the practical approach to the everyday problems of urology is excellent. Particularly impressive is the emphasis on how far the general practitioner should pursue the investigation and care of the patient with a urologic disorder.

Criticisms of the book would include the fact that the urethrogram is not mentioned in regard to diagnosing disruption of the urethra. I also would disagree with some statements in the text; for example, an ectopic ureteral orifice usually does not produce incontinence in men.

M. P. R.

## ► THE PHYSIOLOGICAL BASIS OF MEDICAL PRACTICE

Edited by Norman Burke Taylor, M.D., Professor of the History of Medicine and Medical Literature, University of Western Ontario Faculty of Medicine, London, Ontario, with 30 contributors. Ed. 7. 1,554 pages, illustrated. 1961, The Williams & Wilkins Company, Baltimore. $16.00.

Because of the increased complexity of medical science and the innumerable publications in each of the disciplines of medicine, many of the traditional texts, especially in the fields of internal medicine and surgery, are now written by groups of contributors rather than by single authors. Physiology has passed the point where one or two men can keep abreast of all the new contributions to this subject. Consequently, the new edition of this well-known book has been rewritten by the original authors with the help of many contributors. The familiar format remains unchanged, but the contents of the text have been revised thoroughly and brought up to date, thus ensuring this volume continued popularity as one of the leading books on physiology.

R. V. R.

*(Continued on page A-106)*

BEHAVIOR PROBLEMS IN CHILDREN...

# Mellaril®

THIORIDAZINE HCl

**provides highly effective tranquilization, relieves agitation, apprehension, anxiety**

**and "screens out" certain side effects of tranquilizers, making it virtually free of:**

"The aim of current chemical, pharmacological, and clinical investigations of the phenothiazines is to find derivatives possessing potent and selective tranquilization with a minimum of toxic action.... In agreement with the published results of other investigators, we believe that thioridazine [Mellaril] shows a greater specificity of tranquilizing action and freedom from serious toxic effects when compared with some of the other phenothiazines."[1]

**Behavior Problems In Children:** "At the present time Thioridazine hydrochloride [Mellaril] would appear to increase adaptation and learning of the hyperactive child, in school, at home, and at play. On the basis of this study,* 8 out of 10 hyperactive children placed on a standard dosage of Thioridazine hydrochloride [Mellaril] 10 mg. t.i.d., can remain in school. This improvement has occurred without the appearance of untoward side effects such as: sedation and lethargy...extrapyramidal symptoms...."[2]

Mellaril is indicated for varying degrees of agitation, apprehension and anxiety in both ambulatory and hospitalized patients.

Usual starting dose: Non-psychotic patients – 10 or 25 mg. t.i.d.; Psychotic patients – 100 mg. t.i.d. Dosage must be individually adjusted until optimal response. Maximum recommended dosage: 800 mg. daily. Supply: Mellaril Tablets, 10 mg., 25 mg., 50 mg., 100 mg.

1. David, N. A., Logan, N. D., and Porter, G. A.: Evaluation of Thioridazine (Mellaril), a new phenothiazine, in the hospitalized patient, A.M. & C.T. 7:364, June 1960. 2. Zarling, V. Richard and Hogan, J.: Control of the Organic Hyperkinetic Behavior Syndrome in the Elementary School Child, Scientific Exhibit, American Academy of Pediatrics, Chicago, October 5-8, 1959.

*Study of 21 elementary school "problem" children.

ORIGINAL RESEARCH SERVING THE PHYSICIAN

SANDOZ

## ► BEDSIDE MEDICINE

*By I. Snapper, M.D., Director of Medicine and Medical Education, Beth-El Hospital, Brooklyn, New York. 592 pages. 1960, Grune & Stratton, Inc., New York and London. $14.50.*

In this excellent volume, Dr. Snapper has presented some 50 years of medical practice and teaching. In his introduction, this learned physician states, "Since lip service is still paid to the fame of Hippocrates, this great teacher's concepts of medicine in general, of the practice of bedside medicine in particular, may be quoted here. Hippocrates taught that the greater part of the medical knowledge which the physician must apply at the bedside is based on profound experience in the practice of medicine and clear, logical reasoning about cause and effect."

Medicine travels through various cycles in the course of time. Early in this century, there was a tremendous upswing of the chemical industry; later, animal experimentation and the laboratory were substituted by many physicians for good, common-sense bedside medicine. Dr. Snapper states that at last the pendulum is swinging back to Hippocratic methods, reinforced and enriched by the application of modern laboratory technics. This, he believes, will benefit patients.

The reader of this book gets the impression that he is at the bedside of the patient with the disease being discussed and that Dr. Snapper is talking directly to him rather than presenting a didactic dissertation. For this wonderful approach to bedside medicine and to laboratory worshipers, Dr. Snapper is to be commended.

I. P. F.

**Books received are acknowledged by listing. As space permits, selected books are reviewed more extensively. Listings appear on pages 110 and 170.**

# The Medical Muse

RICHARD ARMOUR

### INSIDE STORY

A "radio pill" which can be swallowed by a patient and tuned in by a doctor to spot trouble in the stomach has been developed.—*American Druggist.*

*This pill, that sends out beeps, not burps,*
*Within the stomach spies and chirps,*
*Informing him who wants to know*
*How things are going there below.*

*With speed of light, or such velocity,*
*It tells of acids, of viscosity,*
*Of pressure changes—that's a fact—*
*And tracks down trouble in the tract.*

*The doctor, meanwhile, makes his set work*
*And listens to this inner network. . . .*
*Now radio; soon there will be,*
*No doubt, intestinal TV.*

### KNOWING THEIR PLACE

There is a difference of opinion among British doctors about where a man should be when his wife is having a baby. One school of thought: right there with her in the delivery room. The other: as far away as possible, preferably in the neighborhood pub.—*News item.*

*A woman's place is in the home,*
*Save when she's in delivery.*
*But where's her husband's, when he waits,*
*All jittery and quivery?*

*Some say his place is by her side,*
*With rubber gloves and mask on,*
*To stand up close and peek and peer*
*And urge the doctor's task on.*

*But others say the pub's the place*
*(They speak with much authority),*
*Or somewhere miles and miles away.*
*(And they're in the majority.)*

# YOUR FINANCES

## FINANCIAL PLANNING FOR THE MEDICAL PRACTITIONER

Mutual funds—a survey of the manner in which these "investment co-operatives" may be used for many investment purposes.

*prepared by*

CEDRIC CAMPBELL

*for*

Postgraduate Medicine

August 1961

The mutual fund too often is regarded as a single investment form with many names – and with one investment company more or less serving the same purposes as another.

For a more accurate view, think of investment companies as being as varied in management, objectives and degree of safety and risk as the individual stocks listed on any exchange.

Each fund has its own investment objectives.

Conservative funds stress safety of capital above all, with moderate income. They will try to hold only highest quality securities.

Growth funds, with their sights on long-term capital growth, may sacrifice present income to gain their objectives.

Income funds seek the highest possible current return.

Speculative funds, aiming for the greatest capital gains, may select speculative issues without undue regard for safety.

Tax-Shelter funds offer investors primarily income with tax advantage or capital gains.

With investment companies now numbered in the hundreds, it would seem that you can find at least one that comes close to filling all of your own investment aims.

In types of holdings, for example, you can easily select funds with any combination of holdings: common stocks only; common and some preferreds; bonds only; bonds, common and preferred stocks; only those stocks issued by companies involved in technological development and production, or securities of companies in one geographical section – Canada, for instance.

This analysis of the portfolio is a simple, mechanical task – one that the fund's prospectus and the mutual fund dealer will help you to perform. At the same time, you can also determine a fund's stated objective (maximum income, safety, long-term growth). This stated policy may then be checked against the fund's record to verify whether it has indeed achieved its objective, and with what degree of success.

Following this analysis, the number of funds suitable for consideration for your own investment purposes now will be seen to narrow down to a manageable number.

* * * * *

"Mutual fund" is the popular name for open-end investment companies. Mutual funds issue only common stock – no other securities (bonds, preferreds) senior to these shares may be issued. The importance of this restriction becomes apparent in the section below devoted to closed-end investment companies. Mutual funds will redeem their shares at any time at current net asset value. A charge of 6-9% made on purchase covers both buying and selling commissions on most funds.

The great – and still growing – popularity of these funds is illustrated by the fantastic growth they have enjoyed from total assets of approximately $1 billion in 1940 to almost $19 billion in 1961.

While it is generally conceded that this growth in large measure has been due to a real service provided to millions of investors, it should be observed that the substantial commissions given brokers for the sale of the funds has hardly been a deterrent to vigorous selling.

* * * * *

Closed-end investment companies differ from their mutual-fund cousins in that they are organized with a fixed-capital structure which can and frequently does include bonds and preferred stock as well as common shares. As a rule, all of the authorized common stock is issued at the initial offering. These shares are then traded on the open market at fluctuating prices subject to the usual brokers' commissions.

> Leverage may be exercised on the common shares when there is a substantial ratio of preferreds or bonds senior to the common stock. How this leverage is applied when the net asset value of the company increases or decreases may be explained simply as follows:

Assume that XYZ Fund has a net asset value of $10 million when you buy your shares in the fund. XYZ has senior securities (bonds, preferreds) with an equity of $6 million. The 100,000 outstanding common shares have a total value of $4 million, or a per-share value of $40. If the net asset value of the fund increases 25% to $12.5 million, the equity of bonds and preferreds remains at $6 million, being a fixed obligation. But the value of the common shares jumps to $6.5 million, for a per-share value of $65 (an increase of 30%). A downside movement of the fund's net asset value would have a similar effect of leverage downward.

> It is evident then that Closed-End Funds financed with a substantial proportion of senior securities are subject to price fluctuations greater than would be the case if only common shares were involved. And it follows that the larger the proportion of existing senior securities above common shares, the more speculative the shares of the fund.

* * * * *

Benefits: It's Mutual. As is the case in most services which you purchase, mutual funds provide many distinct advantages – at a price.

For the average busy professional person thoroughly engrossed in his own field, investment funds are particularly attractive. After the initial selection of one or more funds with investment objectives that match his own, the investor may make additional commitments on a regular basis with a minimum of time and attention. The regularity of his purchases will effect a dollar averaging that can all but ignore price

fluctuations and market conditions. Bookkeeping and the maintenance of records are simplified, since the transactions, dividend income and long-term capital gains will involve a small number of sources and most funds issue well-detailed periodic reports.

The degree of personal supervision may indeed be limited to checking the fund's reports of sales and new purchases to make sure that the fund's investment policy is in fact consistent with its stated policy. And a check on earnings easily reveals whether a generally satisfactory job is being done by the fund management.

Additional features offered:

Diversification – much greater than that usually within the grasp of the average investor. True diversification comprises holdings in a number of different industries (not more than 10% of the fund's capital in any one industry)...in a number of individual companies (less than 5% of its funds in any single company)...and in geographical distribution of the industries and companies.

> It is interesting to observe that in their quest for even more widespread diversification, investment companies have recently been looking beyond domestic industries to foreign shores. Estimates place current fund holdings in foreign securities at over $500 million. A growing number of investment companies currently hold positions in such foreign companies as Philips Lamp Works, Royal Dutch Petroleum, Unilever, Farbenfabriken Bayer, Siemens & Halske and Farbwerke Hoechst.

Protection by government regulation (Act of 1940) against manipulation or other dishonest maneuvers by the fund management.

Liquidity – the fund itself redeems your shares at net asset value at any time. This ready liquidity into cash is not always available in many other investment forms.

Management by professional security and market analysts. Constant supervision and continuous research are always seeking to improve the portfolio (are you in a position to do this for your own holdings?). These professionals also maintain valuable personal contacts with corporation officers as information pipelines.

Tax Benefits – offered by "regulated" funds. These are eligible for exemption from corporate income tax. To comply, the fund, in addition to meeting other qualifications, must pay out total net income and net short-term capital gains every year.

How much for services rendered? The average cost of acquisition is 8% – considerably higher than the cost of both buying and selling other securities. This imposes a limitation. You do not buy investment fund shares for short-term investments; the income and gain in net asset value for a short period would have to be truly sensational to offset acquisition costs.

Add to the "load" charge of buying fund shares the charge for management fees, which usually absorb 10-20% of actual earnings. Generally speaking, the larger funds are able to spread supervision fees over a broader base – your share of the cost is proportionately reduced.

* * * * *

Are mutual funds worth their cost? Many objective studies have attempted to compare investments in funds with similar sums put directly into diversified portfolios. So many "ifs" are involved that they are inconclusive and virtually valueless. The answer is still up to you, the individual investor. You must be able to evaluate your ability to invest on your own. A few bad choices can be disastrous. Modest success averaged down by some poor selections can easily be more costly than the charges made by the funds. On the other hand, results from direct investments equal to the average fund record can save you money.

There may be some value in the thought that professional managers of many trusts, insurance and endowment funds are increasing their holdings of mutual investment shares.

The investor with very limited initial funds (under $5,000) and modest surplus income probably will be well-advised to acquire his portfolio indirectly through a fund.

Where larger sums are involved, the individual must analyze his own ability to buy safely and wisely as carefully as he analyzes any form of investment.

* * * * *

A Congressional inquiry into mutual funds, pending at this time, indicates it will concern itself primarily with management fees and the inexperienced, untrained part-timers selling funds. While the mutual fund industry appears to welcome the probe, it must be amply clear to the investor that buying funds from a well-informed professional who will give equal consideration to <u>all</u> funds with reference to an individual's requirements is certainly preferable to purchasing shares from a sometime salesman who has but one axe to grind.

* * * * *

A word of caution about the innumerable new funds entering the field is necessary. One can hardly generalize against all of these newcomers, but it would seem eminently safer to buy only those funds that have proved their ability to accomplish their objectives over a long period of time. Given a situation where the public is buying its fund shares indiscriminately from salesmen who know little about their product, a temptation exists for an alert mutual fund sales manager to start and sell his own fund. The moral again would seem to be to buy quality, and buy from a fully qualified professional.

* * * * *

IN THE NEXT ISSUE: Which Mutual Fund For You? Specific performance records of some leading funds...how they compare with the general market.

* * * * *

Additional reading on material covered in this article might include: Arthur Weisenberger & Co. manual on mutual funds; "The Intelligent Investor," Benjamin Graham, Harper & Bros., 1959; "How To Plan Your Financial Security," McGraw-Hill Book Co., N.Y., 1949.

*Information contained in these articles is as accurate as careful checking and reliable sources can make it but cannot, of course, be guaranteed.*

# sausage? a problem for your gallbladder patient

For gallbladder patients Entozyme may provide significant relief from the discomforts of fat-induced indigestion. Just six Entozyme tablets (the usual daily dose) digest sixty grams of fat—or more. That's as much as 50 to 90% of the normal daily intake of average adults.

The reason for Entozyme's fat-digestion potency is that each tablet contains 150 mg. of Bile Salts and 300 mg. of Pancreatin, N.F. (in an enteric coating). Bile Salts stimulate the flow of bile and enhance the lipolytic activity of both Entozyme's Pancreatin and the patient's own lipase. Together Bile Salts and Pancreatin greatly aid the emulsification and transport of fat.

Entozyme also contains Pepsin, N.F., 250 mg., which facilitates the breakdown of protein.

**A. H. Robins Company, Inc.,** Richmond 20, Virginia

# entozyme® a natural digestive supplement

# DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

**June 1**—To the Chicago Health Department to meet with our commissioner, Sam Andelman, and W. W. Bauer, N. Fabricant and Lichtenstein to discuss possibilities of organized public health education through the Health Department. In the evening to the Pick-Congress Hotel, where was a great dinner to dedicate the University of Chicago's new diagnostic center. Old Pepys was toastmaster, and introduced Michael DeBakey and Len Scheele. Jonas Salk spoke of the concept of basic science and particularly of the importance of such research in solving the problem of cancer. The meeting ended with an inspiring address by Maurice Goldblatt.

**June 2**—At my desk and conversing with Evelyn Mayer, who is a prize in the field of interior decoration. Then to the Standard Club to dinner. After dinner to see the White Sox play against New York.

**June 3**—To play at golf and in the evening to dine at the Drake Hotel at a great banquet for the benefit of the Hektoen Institute for Medical Research. A beautiful tribute was rendered to the late Daniel Ryan, who as head of the Cook County Commissioners did so much for research. Especially fine was a tribute by Mayor Richard J. Daley. Dr. Samuel J. Hoffman gave a most humorous address on the functions of the director of the Institute.

**June 4**—Early to New York and for luncheon with Mark Soroko and others. Then old Pepys spoke at the dinner in the Grand Ballroom of the Waldorf honoring Judge DiFalco. Jack "Johnny" Carson and Harry Hirschfield, with entertainment from the Copacabana and the Latin Quarter, delighted the audience. A special address was made by Senator Estes Kefauver, who sat next to old Pepys. Old Pepys spoke of the work of the City of Hope and particularly of the necessity for supporting research for many unsolved problems.

**June 5**—Back on the plane and all day at the desk. In the evening with Joe and Minnie Kirsner to the opening of the Moiseyev Ballet, which received one ovation after another for its folk dancing.

**June 6**—At noon to award citations to many workers who participated in the annual "Salute to Medical Research." In the evening to Mrs. Feiwell's, where were Professor Herman Finer; the famous opera singer, wife of the economic counsel of Israel, Madame Daynath; others from the university, and the Orschels, whom we met in Europe.

**June 7**—In the evening with Professor M. Edward Davis and his lady to dine at the President Walk at McCormick Place; then to see again the Russian ballet. This evening was a benefit for Weiss Memorial Hospital and the entire house completely sold.

**June 8**—By early train to Effingham, Illinois, and then driving with Charles Haney to Greenville, where is a jewel of a small hospital with a staff of five physicians; all the specialistic services are provided by consultants from St. Louis. So with Drs. Boyd McCracken, Max Fraenkel and Horton Tarpley to view this beautiful institution, one of its most valuable assets being a recovery room integrated with the operating suites. Thereafter to a cocktail party at the country club, meeting also Drs. Hall and Kaufman. Then to speak to some 400 in the new high school. Driving late with Dr. Harry Cutler, the urologist, to St. Louis and got the airplane well past midnight. Reading en route to Chicago a novel about modern industry and even more modern sex called "The Lion Pit," by Frank Harvey.

**June 9**—In the afternoon came Skolnik from the Chicago Heart Association with two young high school boys—Ehrlich and Rosenstein—who had raised $170 for research on the heart in memory of a young friend who had died following heart surgery. Also conversed with Ken Landauer, who plans to develop a cystic fibrosis foundation. Reading now Harold Robbins' "The Carpetbaggers."

**June 10**—By jet to Los Angeles and with Paul Wermer to the Beverly Hilton. To dine at Petit Jean, where the French cuisine is tantalizing. Then to the home of Dr. Hans Schiff, where were Joseph and Maria Schildkraut and Drs. Bauer, Bay and Steinberg and many other guests.

**June 11**—Walked about and conferred with Mimi Harris on arrangements. To the Grand Ballroom of the Beverly Hilton came some 600 guests for the first Los Angeles Tribute to Medical Progress. Goodwin Knight was chairman and old Pepys was the M. C., introducing Chancellor Sterling of Stanford; Chancellor Murphy, the medico of U.C.L.A., and President Bernard of Claremont Graduate School. They gave citations and awards to Nobel prize winners Chamberlain and Lederberg and to Magoun for his work on the nervous system. Dr. George Piness paid tribute to Harry Karl for his contribution toward founding the Institute for Advanced Medical Learning, of which old Pepys is president. Addresses also were given by Louis Tabak, Paul Wermer and Ben Horowitz of the City of Hope.

**June 12**—At noon came Dr. Sam and Della Pearlman. Then by plane to Fresno to speak for the Executive Club on medical advancement.

**June 13**—Back by plane to Los Angeles, and at noon came my brother Phil with Renee to tell of their son-in-law, Dr. Oscar Entin, of Granada Hills. To dine at Trader Vic's in the best Hawaiian tradition, accidentally meeting Max Cutler.

**June 14**—Up betimes and Gobind Lal came for an interview. Next to luncheon in the restaurant of 20th Century Fox, surrounded by actors and actresses in costumes of various periods. Then chatted for a while with Ken Scott, watching him play the lead in a Western. Thereafter to shop in the Farmer's Market for luscious fruits. Then with Fineman and the Horowitzes to the Wermers', where we enjoyed a real home dinner with the Selbers, Grafs, Sniders, Pinesses and the family, with happy toasts and cultural conversation.

**June 15**—By plane uneventfully back, reading "Mila 18," which is like Hersey's "The Wall," but not as good. From *Time* magazine came Mr. Fraslik

*(Continued on page A-142)*

# 5-year study[1] with COUMADIN demonstrates: long-term anticoagulation in office management of outpatients is practical and effective

A 5-year study[1] of long-term anticoagulation with COUMADIN (warfarin sodium) in office practice patients has demonstrated that such treatment reduces the probability of further infarctions in the postinfarct patient and is effective in preventing a first infarction in patients with angina.

An earlier report[2] noted that long-term anticoagulant therapy with warfarin sodium can be carried out, along with the necessary prothrombin time determinations, as part of general office practice.

**"The most significant advantage is the great ease in maintaining patients in a therapeutic range. It has been rewarding to find, month after month, patients varying no more than three or four seconds in their prothrombin times on their established dosage of Warfarin sodium [COUMADIN]."[1]**

## COUMADIN®

FOR ORAL, INTRAVENOUS OR INTRAMUSCULAR USE

**the original and only warfarin responsible for establishing this drug as closely approaching the ideal anticoagulant[3,4] and as "the best anticoagulant available today."[5] Over 179,000,000 doses administered to date.**

## *the proven anticoagulant for long-term maintenance*

**Full range of oral and parenteral dosage forms**—COUMADIN® (warfarin sodium) is available as: Scored tablets—2 mg., lavender; 5 mg., peach; 7½ mg., yellow; 10 mg., white; 25 mg., red. Single Injection Units—one vial, 50 mg., and one 2 cc. ampul Water for Injection; one vial, 75 mg., and one 3 cc. ampul Water for Injection.

**Average Dose:** Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. Maintenance, 5-10 mg. daily, or as indicated by prothrombin time determinations.

1. Nora, J. J.: M. Times, May, 1961. 2. Nora, J. J.: J.A.M.A. 174:110, Sept. 10, 1960. 3. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958. 4. Moore, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13. 5. Meyer, O. O.: Postgrad. Med. 24:110, Aug., 1958.

*Manufactured under license from the Wisconsin Alumni Research Foundation

*Complete Information and Reprints on Request* Endo **ENDO LABORATORIES** Richmond Hill 18, New York

to discuss background on the American Medical Association.

**June 16**—At the desk and in the evening to dine with Ted Vatz, hearing many fine tales. Late at night watched the *Polizei* in a continuous stream bringing the stabbed, beaten and shot into the Michael Reese Dispensary—Outpatient Department, they call it—and I would be out of patience with this problem.

**June 17**—Came again Fraslik from *Time* for an interview. In the evening to Phil Winston's for a fine dinner with the Byerrums.

**June 18**—To visit the youngsters for Father's Day, and lunched with the Marks family. Later to dine at the Villa Moderne, now Allgauer's, and then home, accompanied by great bouquets of peonies.

**June 19**—Reading now "Memoirs of a Medico," by Dr. E. M. Alonso of the Castellana Hilton, which has much excitement and interest—but not all of his memoirs.

**June 20**—At noon to O'Hare to fly to Bay City. With Haney driving to Harbor Beach to view the hospital which will be rebuilt into modern facilities. Thereafter to the home of Dr. P. L. Turner for cocktails and then to speak to some 400 in the Zion Lutheran School. Back by car to Bay City.

**June 21**—By an early Viscount to Chicago. In the afternoon came Floyd Landis to speak of research and development, and all day the long-distance telephone trilled.

**June 22**—In the morning came Arthur Siegel, the *Time* photographer, to snap various poses of old Pepys. All afternoon at the desk in readiness for the trip early next day to New York.

**June 23**—To New York, reading en route a mystery of a man who laughed at death, and it was not funny. In the evening with all the Friedells to dine at Lindy's, and saw there the Hamiltons, with their daughter, and the Piczeks, which was like a family reunion.

**June 24**—To the meeting of the American Geriatrics Society, which was designed for the public, with Bortz expounding the problems of the aged. Then to the New York chapter of the American Medical Writers' Association to hear Russell Cecil, E. di Cyan, Bill Laurence, David Lyall, Bill White, Cooper, Graupner and McCleery range the whole world of medical writing. Here were Lois Stice, Bob Potter and many other associates. At noon to dine with Russell Cecil and Di Cyan for further discussions.

**June 25**—To the meeting of the editors of *World-Wide Abstracts*, being greeted by Len Scheele and Al Driscoll. Engaged in a fine discussion of many aspects, particularly surgical and psychosomatic, with Ravdin and Jack De Tar in a pleasant debate. At noon all to the Alisa V, where Elmer Bobst provided a fine luncheon and a sail up and down the river.

**June 26**—To luncheon with the editors of *Medical World News*, where were Geffen, Silver, White, O'Neill, Rusk, Diehl, Keefer and Van Dellen to discuss every aspect of medicine. Then to see the exhibits, and from there to the Essex House, where Teresa Cohen and Sylvia Covet entertained a multitude for POSTGRADUATE MEDICINE, and traded tales with Vic Lowrie and Fred Couzens, also of this Journal.

**June 27**—To the exhibits, and then with William Crookes presiding to address the medical exhibitors at their annual meeting. Then to the Plaza, where Richard Nixon spoke to the Pharmaceutical Advertisers Association and Elmer Bobst introduced him. Later to Howard Rusk's new apartment on Beekman Place, which is just opposite Mary Lasker's. Here were the Rusk family and Vernon Luck from Los Angeles.

**June 28**—For breakfast came Stanley Henwood; then to Doubleday's and with Runyon and Winslow to meet Geffen and Lasdon at the Hemisphere Club to formulate a new book on research. Here saw Bennett Cerf with Nichols of *This Week* magazine. In the evening to the Schering cocktail party, where some time was spent in conversation with Harry Weaver, Fagan, David and Dorothy Dietz and Marguerite Clark. Next to the Passano award dinner, where all testified to the contributions of Owen Wangensteen, who graced the dais with his charming lady, Sally. These dinners each year are an assemblage of the leaders of many phases of medical science and education. Four pupils and Maurice Visscher gave eulogies. Then to the Skytop Room of the Statler-Hilton, where came the Silver Slipper Club. Elmer Bobst presided and introduced the president and president-elect of the American Medical Association.

**June 29**—In the morning to view again the scientific exhibits with Bill Lasdon and Al Driscoll. In the afternoon came Drs. Charles McClave and Don Hosier of Columbus, Ohio; William Howard of Washington, D. C.; H. H. Shuman of Springfield, Massachusetts, and Alvan Barach of New York to confer on respiratory disorders of children. After some hours of discussion to the studio, where was made a record of the panel to be distributed by Borden's for pediatricians. Next to the Waldorf, where Peter Warren and old Pepys for *Excerpta Medica* entertained some 70 guests.

**June 30**—Early in the morning to confer with Teresa Cohen and Sylvia Covet. Mistress Pepys departs for Idlewild airport. In the afternoon came Dr. Milton Helpern, Chief Medical Examiner of New York City; the pathologist Nickerson of Boston University; Edith Potter of Chicago Lying-in Hospital, and Coe of Minnesota to consider the causes of sudden death in infants and to make a tape recording. Thereafter, the evening being warm, old Pepys relaxed with the newsreels and went early to bed.

### FROM THE JOURNALS

"It is jokingly stated that if you go away for the week end you are out of date on Monday, and there is an element of truth in this."—*Dr. K. W. Donald, University of Edinburgh.*

* * *

"We must not organize the whole of medical education as if every student is a potential Nobel prize winner."—*Dr. K. W. Donald, University of Edinburgh.*

* * *

### AS FAR AS IT GOES

She sat in the witness stand, legs crossed comfortably for her—slightly uncomfortably for everyone else.

The prosecuting attorney said, "Your Honor, may I be pardoned a moment? I just thought of something!"

"Of course," said the judge, "so has every other man in the courtroom."

* * *